DOCTOR OF MEDICINE

Prevalence of left ventricular hypertrophy in peripheral arterial disease and its relation to blood pressure

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PREVALENCE OF LEFT VENTRICULAR HYPERTROPHY IN PERIPHERAL ARTERIAL DISEASE AND ITS RELATION TO BLOOD PRESSURE

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Contents

ABBREVIATIONS

AII	Angiotensin II
ABPM	Ambulatory Blood Pressure Monitoring
ASE	American Society of Echocardiography
BNP	B-type natriuretic peptide
BSA	Body surface area
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
ECG	Electrocardiogram
LV	Left ventricular
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMI	Left ventricular mass index
LVEF	Left ventricular ejection fraction
IVS	Interventricular septal wall thickness
LVIDD	Left ventricular internal diameter during diastole
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
PWT	Posterior wall thickness
RWT	Relative wall thickness

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Statistical analysis of the Study data was performed with the help of Dr Donald Ang, Research Fellow, Department of Clinical Pharmacology, Ninewells Hospital

Declaration

I herby declare that:

a) I gained ethical approval for the study from the Tayside Committee on Medical Ethics.

b) I recruited all the patients in the Study and performed all the investigations including the echocardiolgram, physical examination, questionnaire and 24 hour blood pressure monitoring.

c) I am the author of this Thesis

d) All references have been consulted by me

e) The work of which the thesis is a record, has been done by me

f) This Thesis has not previously been accepted for a higher degree

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Gary A Wright Date

Abstract

Objectives: To assess the prevalence of left ventricular hypertrophy (LVH) in patients with newly diagnosed peripheral arterial disease (PAD).

Methods: Consecutive patients referred for the first time for assessment of PAD with a history of intermittent claudication and ankle brachial pressure of index of ≤0.9 were recruited. All subjects underwent a full echocardiogram, office blood pressure and 24 hour ambulatory blood pressure monitoring.

Results: Out of 350 subjects screened, left ventricular mass measurements were available on 227 (65%). The prevalence of LVH indexed to body surface area was 50%. In a multiple regression model the factors independently related to LVH were age, sex and history of diabetes. There was no relation between presence of LVH and 24 hour blood pressure.

Conclusion: LVH is prevalent in patients with PAD and is not associated with 24 hour blood pressure.

Papers arising from this Research

Wright GA, And DS, Stonebridge PA, Belch JJ, Struthers AD. Left ventricular hypertrophy is present in one half of newly disagnoses peripheral arterial disease patients. *Journal of Hypertension, 2007; 25(2):463-469*

Ang DS, Fahey TP, **Wright GA**, Struthers AD. Development and validation of a clinical score to identify echocardiographic left ventricular hypertrophy in patients with cardiovascular disease. *American Journal of Hypertension. 2008;21(9):1011-1017*

HYPOTHESIS

Peripheral Arterial Disease (PAD) is a common condition, affecting approximately 3 to 25% of the population and this group of patients are known to be at high risk of premature death (1-6). It is generally thought that this is exclusively due to coincidental coronary artery disease, which leads to cardiac death due to ischaemic events. While this is likely to be a major factor, left ventricular hypertrophy (LVH) is potentially a second major contributor to cardiac death in these patients but little attention is routinely paid to this added risk factor (7). LVH is an important predictor of cardiovascular risk and studies in the comparable vascular disease of angina, suggest that left ventricular hypertrophy poses a bigger risk of cardiac death than multivessel coronary disease with a relative risk of 2.4 for LVH and 1.6 for multivessel coronary artery disease (CAD) (7).

LVH is known from all population studies to be a strong independent risk factor for cardiovascular death but what we do not yet know is how common LVH is in PAD patients (8-12). To have a significant impact on a condition, the risk factor should be common. There are several reasons to believe that LVH might be common in PAD paients.

Firstly, by its nature, PAD is associated with stiff arteries, which increases left ventricular (LV) afterload and in theory promotes LVH.

Secondly, in patients of similar high cardiovascular risk, data shows that LVH is remarkably common. Data from this institution (University of Dundee) demonstrated that 52% of angina patients, 42% of type 2 diabetics, 25% in a random group of stroke survivors and 25% in a random group of patients attending a geriatric day hospital have evidence of LVH (13, 14).

Thirdly, PAD patients have an increased incidence of renovascular disease (overt and subclinical) which increases Blood Pressure (BP) and thereby promotes LVH.

Fourthly, often a vascular surgeon is the only specialist to see a PAD patient and they may understandably focus more on surgical possibilities than on the pharmacological management of these patients BP or secondary cardiovascular protection.

If LVH does turn out to be common in PAD patients, then detecting and treating it could be a major new way to reduce cardiac deaths in this group of with high mortality and morbidity. This possibility arises because LVH regression has been shown to strongly improve prognosis, irrespective of BP changes (15). Indeed, it appears that full LVH regression returns risk to that of someone with no LVH (12, 16).

In this study I set out to assess how LVH is prevalent in PAD patients and to elucidate its relation to blood pressure.

CHAPTER 1

INTRODUCTION

1.1 PERIPHERAL ARTERIAL DISEASE

1.1.1 DEFINITION AND PREVALENCE

The American Heart Association/ American College of Cardiology (AHA/ACC) 2005 Practice guidelines for the management of patients with peripheral arterial disease state: "The term "peripheral arterial disease" includes a diverse group of disorders that lead to progressive stenosis or occlusion, or aneurysmal dilation, of the aorta and its non-coronary branch arteries, including the carotid, upper extremity, visceral, and lower extremity arterial branches." (17)

Historically, the term "peripheral vascular disease" has been most used to describe the noncardiac diseases that affect the circulation as a whole. This term encompasses numerous pathophysiological syndromes that affect the arterial, venous, and lymphatic circulations. It therefore includes all vascular diseases that alter organ perfusion. Arterial diseases include those disorders that cause either fixed obstruction or abnormal vascular reactivity of the arterial supply to a given tissue. This can lead to impaired blood delivery and produce ischemia.

PAD is very common in the western world and a recent systematic review of the literature demonstrated that contrary to common belief, it is just as common in low and middle income countries than in the more affluent parts of the world (6). Estimates of the prevalence of peripheral arterial disease vary widely, from 3% to 57%, depending on how the disease is identified and

the populations studied (2, 5, 6, 18-34). PAD is just as common in females as it is in males; indeed it is more prevalent in females in some age groups compared to their male counterparts. In both sexes the prevalence increases from 2.7% in those aged 25 to 29 years to 24% in those aged above 95 years in the same proportion in high income countries (HIC) (6). In low and middle-income (LMIC) countries the prevalence increases from 1.2% in males and 4% in females at age 25 to 29 years to 21.5% in males and 18.6% in females at age over 95 years. The prevalence of PAD in females from age 25years to 64 years is approximately double that of their male counterparts in low and middle-income countries. Rates of newly diagnosed disease are in the range of 7% to 13% per year (28). The proportion of people with PAD has increased by up to 50% worldwide, with most of this increase occurring in low and middle-income countries (6). PAD can be progressive, with about a third of patients reporting worsening symptoms that require surgical interventions over 5 to 10 years (17).

1.1.2 PATHOGENESIS AND RISK FACTORS FOR PAD

PAD typically refers to the atherosclerotic process that involves the lower extremities, commonly the aorta and ilio-femoral arteries. Atherosclerosis is a complex process involving vascular remodeling, inflammation, oxidative stress, thrombosis, platelet aggregation, lipid abnormalities and endothelial disturbance. Similar to the analogous process of coronary atherosclerosis, this process involves a number of stages including lesion initiation with endothelial dysfunction, fatty streak development, fibroproliferative

atheroma, lipid rich core with fibrous cap and intimal hyperplasia. This causes remodeling and intrusion into the lumen of the artery causing claudication (angina of the leg muscles). Claudication symptoms occur due to mismatch between oxygen requirements and delivery to the skeletal muscles of the lower limbs. This process is usually insidious but the presence and severity of symptoms can be related to other factors. These factors include endothelial function, collateral blood supply, oxygen delivery, muscle mechanics and energy metabolism and patient comorbidities. Acute occlusions occur when there is disruption of the fibrous cap, resulting in exposure of the necrotic lipid rich core and subendothelial tissue resulting in thrombus formation and acute ischaemia.

PAD is a marker for generalized systemic atherosclerosis and it has typical cardiovascular risk factors such as advanced age, cigarette smoking, diabetes mellitus, hypercholesteroaemia, and hypertension (6). In addition to age with an odds ratio of 1.39, several risk factors showed a consistently significant association with PAD in both HIC and LMIC. Smoking was the strongest risk factor with an OR of 2.1 for all countries, and diabetes a close second with an OR of 1.68. Almost every study on PAD has reported an important link with hypertension, with 50% to 92% of subjects having a history of arterial hypertension (5, 27). The Framingham study demonstrated a 2.5 to 4-fold increase in the risk of developing PAD in subjects with hypertension (35).

As well as the traditional cardiovascular risk factors, other factors have been demonstrated to be important in PAD such as race and ethnicity, genetics and

abnormal hip to waist ratios (**Table 1.1**). There are well-recognized differences in cardiovascular disease in different ethnic groups. Although South Asians living in the UK have a worse risk factor profile and greater risk of coronary artery disease than the Caucasian population, they have a lower prevalence of PAD and lower limb amputation rates (36, 37). Caucasians have a higher incidence of abdominal aortic aneurysm. The reason for this discrepancy is not clear and it is not know whether PAD disease distribution is due to genetic or environmental differences. It is known that South Asians have a higher mortality from CAD than the Caucasian population and it may be that South Asians don't live long enough to develop symptomatic PAD; given that PAD is strongly associated with age (37). To date, no major gene has been discovered for PAD, although observational studies suggest an increased rate amongst healthy relatives of patients with claudication (38).

Table1.1 Risk Factors for Peripheral Arterial Disease

Traditional	Non-Traditional
Advanced Age	Race/Ethnicity
Smoking	Genetics
Diabetes & Impaired Glucose Tolerance	Inflammatory Markers (CRP, Fibrinogen, IL-6)
Hypertension	Hypercoagulable States
Dyslipidaemia	Abnormal hip to waist ratio
	Homocysteine
	Chronic Kidney Disease
	Metabolic Syndrome

1.1.3 PROGNOSIS OF PAD (MORTALITY AND MORBIDITY)

Compared to the large publicity and public health initiatives on myocardial infarctions (MIs) and strokes, public recognition of the risks, symptoms, morbidity and mortality associated with PAD has been largely neglected. A number of studies suggest that risk factor management is treated less aggressively in those patients with PAD as opposed to those with CHD (5, 39). The prevailing evidence shows that PAD is a worldwide disease and its prevalence has increases by almost 50% over the last 10 years. This represents a significant public health problem, given the increased mortality and morbidity associated with PAD (40, 41).

PAD is strongly associated with age and has the same traditional cardiovascular risk factors as MI and stroke. The prevalence of coronary heart disease in patients with PAD is between 14% and 90%, depending on the population screened and tests used (2, 30, 42-44). The prevalence of cerebrovascular disease varies just as wildly. Depending on how it is quantified it ranges from less than 20% in those diagnosed from symptoms to 80% in those with a stenosis of a major head and neck artery of >30% (3, 4, 21, 22, 27, 34, 45-47).

A large retrospective study performed in Canada over a 10-year period from 1985 to 1995, demonstrated that the annual mortality was higher among patients with symptomatic PAD (8.2%) than those with a prior myocardial infarction (6.3%) (28). The investigators compared outcomes of the PAD

cohort (16,440 patients) to reference populations with a first diagnosis of myocardial infarction (15,590 patients) and stroke (18,704 patients). 10% of the PAD population suffered a subsequent stroke, a further 10% had an MI and almost half were dead (**49%**) within the mean follow-up of 5.9 years. This compares to a mortality rate of **40%** in the MI group and **49%** in the stroke group. Broadly similar findings have also been reported in previous studies involving patients with PAD symptoms (32, 46, 48-52). This compares impressively with a recent meta analysis of four large cardiovascular trials in post MI and heart failure patients (CAPRICORN, VALIANT, EPHESUS and OPTIMAAL) (53). In this meta analysis 28,771 patients were analyzed with a PAD prevalence of 8.2%. Over a mean follow up of 2.7 years **18.8%** of these patients died and **52.3%** experienced a composite of cardiovascular death or hospitalization. In patients with PAD the adjusted **HR** for heart failure hospitalization was **1.37** and all cause mortality of **1.26** (53). The model controlled for the following covariates: age, gender, race, systolic blood pressure, BMI, smoking history, Killip class, history of diabetes, hypertension, angina, MI, Atrial fibrillation, dyslipidaemia, renal insufficiency, heart failure, chronic obstructive pulmonary (COPD) and stroke. Even adjusting for all these factors, PAD was strongly associated in a multivariate model, with all cardiovascular morbidity including, CV hospitalizations, heart failure, MI, and all composite endpoints with an adjusted **HR** of between **1.17** and **1.52**. The strongest association was with subsequent MI. Surprisingly; the only CV endpoint that was not statistically increased in a multivariate model was that of stroke, although it was in a univariate model. These figures are consistent with other studies, including

the Global Registry of Acute Coronary Events (GRACE), where the prevalence of PAD was 9.7% in 41,108 participants with acute coronary syndrome (54).

The increase in cardiovascular risk in those with PAD was dependent on the number of additional risk factors at the time of diagnosis, illustrating how risk factors are additive, resulting in a 'cumulative' cardiovascular risk that parallels cardiac disease. The risk of myocardial infarction was significantly increased in those aged over 65 years, especially with concomitant angina, diabetes mellitus, heart failure, and hypertension.

Having PAD confers high cardiovascular risk, which is comparable to populations of patients with prior MI and stroke, and this message needs to be emphasized. Importantly, the majority of PAD subjects remain asymptomatic but constitute a high-risk population. Of concern, risk factor reduction in those with a diagnosis of PAD is less frequently applied in comparison to those with cardiac disease. Thus, PAD patients may have had a less intensive risk reduction, leading to an increased cardiovascular event rate.

PAD commonly presents in secondary care to vascular surgeons in the UK and the onus is on them to initiate full cardiovascular risk prevention therapies, such as smoking cessation and the aggressive treatment of hypertension and lipids. However, many PAD patients also have cardiac problems, and may attend hypertension and lipid clinics. Perhaps the time has come to organise vascular clinics jointly run by vascular surgeons and cardiovascular physicians, as one possible solution. The approach to the PAD patient should not simply be surgical but should include intense focus on

aggressive risk factor identification and modification (5, 17, 31, 51, 55, 56).

As in cardiac disease, blockade of the renin-angiotensin-aldosterone system (RAAS) may offer another therapeutic target. For example, in the Heart Outcomes Prevention Evaluation (HOPE) study, 44% of the study population (patients at high risk of cardiovascular events including patients with cardiovascular disease, diabetes and age >55 years) had PAD and an impressive reduction in cardiovascular events was seen in the ACE inhibitor (Ramipril) group. This reduction was independent of blood pressure reduction (57).

In summary, there is now growing evidence that PAD patients are a high-risk group, although still relatively under detected and under treated. This is despite the fact that they have an increased mortality rate comparable to those with pre-existing or established cardiovascular disease (myocardial infarction, stroke).

1.1.4 MANAGEMENT OF PERIPHERAL ARTERIAL DISEASE

The importance of risk factor management in patients with PAD is less well appreciated compared to those patients with coronary artery or cerebro-vascular disease and is treated less aggressively. The Scottish Intercollegiate Guidelines Network (SIGN) and National Institute for Health and Clinical Excellence (NICE) guidelines mandate that patients with PAD should be seen in a cardiovascular clinic and have a cardiovascular risk factor assessment.

The overall management in this group of patients involves reducing cardiovascular events through risk factor optimization, preventing progression of PAD and limb loss and improving symptoms and general wellbeing thorough counseling, pharmacological medication, exercise programs and surgery or vascular endovascular intervention where required.

1.1.4.1 Blood Pressure Optimization

Hypertension is an established risk factor for mortality and morbidity and that adequate treatment reduces cardiovascular risk in the population. Blood pressure control in PAD patients is supported by the Heart Outcome Prevention Evaluation study (57). The ACE inhibitor Rampril resulted in a 20% relative risk reduction in MI, Stroke and vascular death. Beta blocker therapy is advocated in patients with coronary disease and there is no evidence of worsening of claudication in patients with PAD, despite previous historical concerns regarding this side effect (58).

1.1.4.2 Anti-platelet Therapy

The antiplatelet agent Aspirin has been strongly advocated in all guidelines. Aspirin may reduce the occurrence of acute cardiovascular events by decreasing the risk of thrombus formation. A meta analysis performed by the Antithrombotic Trialists' Collaboration demonstrated a significant benefit from daily anti-platelet agent use in patients at high cardiovascular risk. In a subgroup analysis of PAD patients, there was a statistically significant 23% reduction in major vascular events in the group taking anti-platelet therapy (59). A recent randomized controlled trial assessing the efficacy of low dose

aspirin in patients with PAD demonstrated a 26% reduction in vascular events compared to patients not taking aspirin (60). In a subgroup analysis of the CHARISMA trial, dual anti-platelet therapy with the combination of aspirin and clopidogrel versus aspirin alone showed no benefit in the composite end point of MI, stroke and CV events (61). Therefore, single agent anti-platelet agents are recommended for prevention of CV events in patients with PAD.

1.1.4.3 Lipid Lowering Therapy

The use of lipid lowering therapy and in particular, HMG-CoA reductase inhibitors (Statins) such as Simvastatin and Atorvastatin, has been associated with a significant improvement in outcome in primary and secondary cardiovascular patients. Less is known about the benefit of these agents in patients with peripheral arterial disease compared to the extensively studied group of patients with cardiovascular and cerebrovascular disease. A subgroup analysis of PAD patients in the Heart Protection Study demonstrated a 22% relative risk reduction in the rate of first major vascular events in the group taking Simvastatin, regardless of baseline LDL level (62). Moreover, there is evidence that these agents improve symptoms of claudication and increase walking distance (63). Therefore, lipid lowering with a statin is recommended for patients with PAD and a total cholesterol of >3.5mmol/l.

1.1.4.4 Smoking Cessation

Smoking is one of the most potent risk factors for the development of PAD. It has a 2 to 6-fold increase in the risk of developing PAD with a dose-response

effect (64). Patients who smoke also have a worse outcome, with higher rates of critical limb ischaemia and amputation. Smoking cessation improves survival and improves exercise capacity; this is evident even after 1-year of abstinence (65). Smoking cessation is therefore at the foundation of risk reeducation in this group of patients.

1.1.4.5 Exercise Therapy

Patients with symptomatic PAD have reduced exercise capacity and quality of life. Supervised exercise programs have consistently been shown to improve walking performance, claudication severity and quality of life. A Cochrane review and meta analysis of trials comparing supervised and unsupervised exercise therapy in patients with symptomatic PAD showed that supervised exercise produced significant improvements in walking distance of between 60% to 337%, compared to unsupervised exercise (66). Therefore, in all guidelines, patients with PAD and intermittent claudication should be encouraged to partake in supervised exercise.

1.1.4.6 Summary

PAD is an under diagnosed and undertreated condition and is associated with a profound increase in mortality and morbidity. Claudication is a marker of systemic atherosclerosis which mandates aggressive risk factor management and intensive medical therapy. This is not always achieved in the primary or secondary care setting. The therapeutic interventions that should be implemented include:

Antihypertensive Therapy

Lipid Lowering Therapy

Antiplatelet Agents

Smoking cessation

Supervised Exercise Therapy

These measures not only improve symptoms and quality of life but also significantly reduce cardiovascular events.

1.2 PATHOGENESIS OF LEFT VENTRICULAR HYPERTROPHY

1.2.1 PATHOPHYSIOLOGY

Left Ventricular Hypertrophy (LVH) is thought to be a structural adaptation of the heart, at least in part, as a compensatory mechanism for increased blood pressure and wall stress (i.e. increased mechanical load such as increased blood pressure and aortic stenosis) (67).

The heart is able to compensate for haemodynamic burden by:

1) Using the Frank-Starling mechanism to increase contractility

2) Employing hormonal mechanisms to increase contractility

3) Increasing muscle mass to bear the extra load

The first mechanism is limited physiologically and the second has been shown to be deleterious chronically, such as in heart failure. Increasing cardiac muscle mass has a key compensatory role in haemodynamic overload. This increase in mass is due to hypertrophy (increase in size) rather than hyperplasia (increase in number) of cardiac myocytes. Cardiac muscle hypertrophy is the chronic adaptation of the left ventricle to increased cardiac load. Increased wall stress provides a stimulus for increased mRNA

transcription of myocyte proteins. Studies performed on the pathways that can lead to the increased protein synthesis that causes LVH have provided evidence that LVH may occur in the absence of recognisable changes in cardiac loading conditions (68-70).

It is believed that mechanical signals initiate a cascade of biological events leading to cardiac growth and hypertrophy. Hypertrophy is usually accompanied by complex changes in gene expression. These changes include the re-expression of immature foetal cardiac genes, variable expression of genes that modify intracellular ion homeostasis and important parasympathetic and sympathetic receptors are down regulated (e.g. down regulation of α_1-adrenergic receptors, M2 muscarinic receptors and increase in ratio of angiotensin-II AT2 to AT1 receptor subtypes). However, the long-term implications of these changes in gene expression are still unclear in vivo (68-71).

After birth, the myocytes lose their ability to proliferate (increase their numbers). Subsequent growth therefore occurs as a result of enlargement of preexisting myocyte cells. Myocardial gene expression is up regulated in the initiation of ventricular hypertrophy, although the precipitating factors involved in this up regulation are not well understood. A number of molecular risk factors for hypertrophy including modulation of the renin-aldosteone-angiotensin system (RAAS), growth factors, natriuretic peptides, endothelin, and the cardiac myosin heavy chain genes have been reported (68-71).

Hypertension has long been implicated as one of the most important underlying causes of LV hypertrophy. Other factors implicated include:

- obesity,
- age,
- dietary sodium intake,
- volume load,
- diabetes,
- arterial hypertrophy and stiffening (pressure overload),
- insulin resistance, and
- neurohumoral factors (e.g., adrenergic factors and the renin-angiotensin-aldosterone system).

Many of these factors differ across ethnic groups, and may partially account for the observed differences in LV hypertrophy across populations. Given the number of potential determinants of LV hypertrophy, there are likely to be several genes acting independently or synergistically to increase risk for LV hypertrophy.

1.2.2 SIGNALS FOR CARDIAC GROWTH

The search for a chemical signal that serves as a master switch for cardiac growth has so far proved fruitless. Multiple kinases that are implicated in hypertrophy are located within the extracellular matrix (ECM) of cardiac myocytes. It appears that angiotensin II, via the AT1 receptor, plays a crucial role in the induction of hypertrophy as this hormone can induce the molecular events of early cardiac growth in mammals (68, 69, 71). However, the

observation that pressure overload produces cardiac hypertrophy in AT1 receptor knock-out mice suggests that there are other important mechanisms. The pathways through which different stimuli increase LV mass are unknown but likely involve expression of numerous genes and cardiac transcription of neorohormones including angiotensin-II, aldosterone and endothelin (72, 73). Neurohormones have both haemodynamic activity (e.g. increase blood pressure, reduce sodium excretion) and are direct growth factors. Studies suggest that the process of hypertrophy begins at the time of increased mechanical strain and progresses through its compensatory stage to a pathological stage leading to an increase in LV mass, which is deleterious. It is clear that the signals involved in the initiation and perpetuation of ventricular hypertrophy are complex and not well understood. It is beyond the scope of this thesis to discuss in detail, the molecular and genetic basis for left ventricular hypertrophy.

1.2.3 LVH AND PRESSURE AND VOLUME OVERLOAD

1.2.3.1 PRESSURE OVERLOAD

In response to pressure overload in conditions such as aortic stenosis or peripheral arterial hypertension, the parallel addition of sarcomeres causes an increase in myocyte width (not number), which in turn increases wall thickness. This remodeling results in concentric hypertrophy (increase in ratio of wall thickness/chamber dimension).

A principle of physics is that the tension on the wall of a sphere is the product of the pressure times the radius of the chamber and the tension is inversely related to the thickness of the wall.

According to the law of LaPlace, the load on the myocardium is given as follows:

$$\frac{\text{Pressure x Radius}}{\text{Wall Thickness}}$$

Therefore, an increase in pressure can be offset by an increase in wall thickness.

1.2.3.2 VOLUME OVERLOAD

Volume overload in conditions such as chronic aortic valve regurgitation, mitral valve regurgitation, anemia or renal failure, creates myocyte lengthening by sarcomere replication in series and therefore an increase in ventricular volume (74, 75). This pattern of eccentric hypertrophy (cavity dilatation with a decrease in ratio of wall thickness/chamber dimension) is also initially compensatory. The heart can meet the demand to sustain a high stroke volume. However, chronic hypertrophy may be deleterious because it increases the risk of developing heart failure and consequently premature death (76).

1.2.4 HYPERTROPHY AND CONNECTIVE TISSUE

For myocyte growth to support an increased mechanical load, it must be accompanied by increases in the surrounding extra cellular matrix architecture of connective tissue and ground substance, as well as the capillary and nerve networks. The connective tissue itself is primarily composed of collagen with smaller amounts of elastin, laminin, and fibronectin. Although collagen types I, III, and V are found in the myocardium, type I comprises 85% of the total collagen in this location. The complex collagen weave provides a mechanism for translating individual myocyte force generation into ventricular contraction, it controls the development of cardiac interstitial edema, and it is responsible for much of the ventricle's passive diastolic stiffness. Autopsy

and biopsy studies of patients with severe pressure overload in the form of chronic hypertension or aortic stenosis frequently show changes in collagen architecture. This is manifest as significant increases in the percentage of fibrosis occupying the myocardium (77, 78). Therefore, ventricular hypertrophy is as a consequence of both myocyte growth and increase in extra cellular matrix. This is initially compensatory but then leads to deleterious effects physiologically.

1.3 ECHOCARDIOGRAM AND LEFT VENTRICULAR HYPERTROPHY

1.3.1 LV Mass Measurements

In clinical practice, LV chamber dimensions are used to derive measures of LV systolic function, whereas in epidemiological studies and treatment trials, one of the largest applications of echocardiography has been the estimation of LV mass in populations and its change with antihypertensive therapy. All LV mass algorithms, whether using M-mode, 2D, or 3D echocardiographic measurements are based on subtraction of the LV cavity volume from the volume enclosed by the LV epicardium (outer surface) to obtain LV muscle volume. This volume is then converted to mass by multiplying by myocardial density. Following this principle, several methodologies have been used to calculate left ventricular mass and to define hypertrophy. Each method has its own flaws and strengths at each step, all of which results in a wide range of values.

Critical Steps in Determining and Interpreting Left Ventricular Hypertrophy using Echocardiography

1. Imaging – Mode and Acquisition
2. Estimating Left Ventricular Volume
3. Defining Border Limits
4. Calculating Mass – LV Mass Formulas
5. Indexing for Body Size
6. Determining Cut-off Points
    a. Using a reference sample (normality/statistical criteria)
    b. Using prognostic data (driven by clinical endpoint)
7. Evaluation of Left Ventricular Structure

The most significant echocardiographic limitation is related to inadequate image quality. Population-based studies using standard trans-thoracic echocardiography are not able to obtain complete images in almost a quarter of screened patients mainly due to inadequate acoustic windows and poor endocardial definition (79).

1.3.2 Imaging Mode and Acquisition

LV mass can be calculated using M-mode and 2D imaging, although M-mode imaging allows better endocardial border definition as it has greater resolution due to higher frame-rate (80). To date, most LV mass calculations in studies and guidelines have been made using 2D targeted M-mode measurements.

1.3.3 Defining Endocardial Borders

Ultrasound signals are enhanced where surfaces change density and this allows definition of edges. The exclusion or inclusion of these signals from myocardial interfaces can cause significant discrepancies in the overall measurements. Initial M-mode standards recommended measurement from the leading edge (nearest the echo probe) to trailing edge (edge further from echo probe) in the septum and from leading edge to leading edge of the posterior wall. The Penn Convention Criteria excludes echos from the wall boundary edges. This approach underestimated LV mass when compared to the most accepted border definition criteria of the American and European Societies of Echocardiography criteria, which measure leading edge to leading edge (**Figure 1.1**) (79).

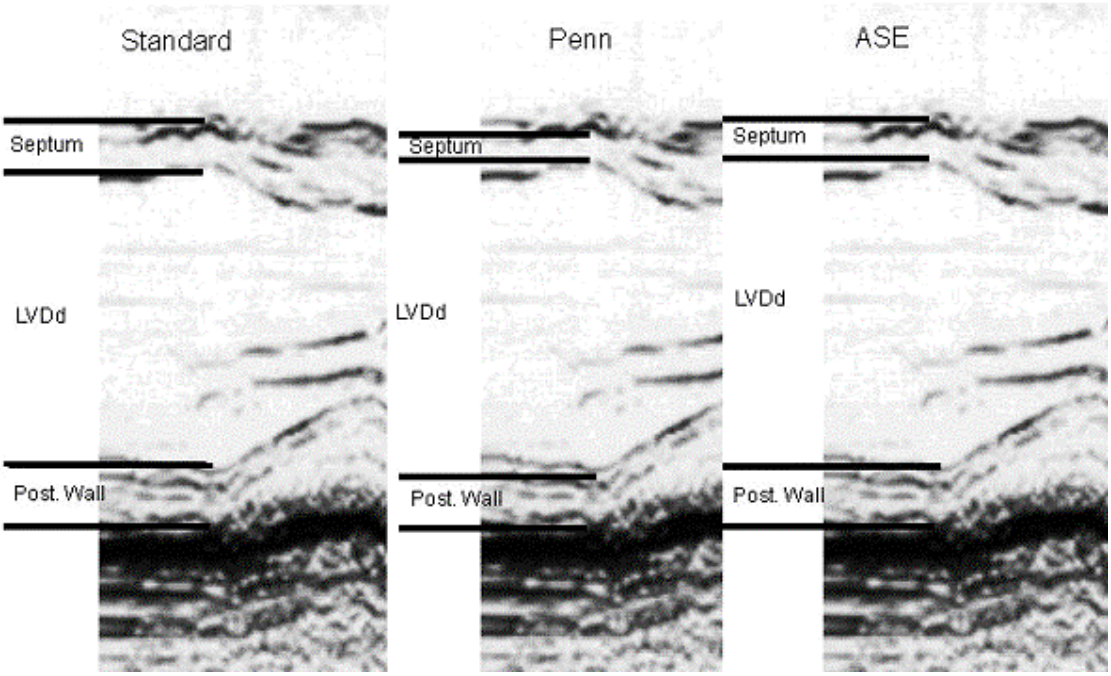


Figure 1.1 Echocardiographic Endocardial Definition of Left Ventricular Mass Formulas. (Image from Foppa et al 2005) (79)

The **Standard convention** used the leading edge to trailing edge in the septum and leading edge to leading edge in the posterior wall.

The **Penn formula** excludes all echoes from all walls and uses the trailing edge to leading edge in the septum and posterior walls

The **ASE criteria** use leading edge to leading edge in all walls

ASE – American Society of Echocardiography

LVDd – Left Ventricular Dimensions in diastole

1.3.4 Calculating LV Mass – LV Mass Formulas

Formulas to estimate LV mass are variations on the same mathematical principle. Where LVIDD, PWTD and IVSD are Left Ventricular Internal Diameter in Diastole, Posterior Wall Thickness in Diastole and Septal Wall Thickness in Diastole, respectively. Original calculation from Troy were the first to be recommended (81):

TROY FORMULA:

$$\textbf{LV Mass} = 1.05\,((\text{LVIDD} + \text{PWTD} + \text{IVSD})^3 - (\text{LVIDD})^3)\text{g}$$

DEVEREUX FORMULA 1:

Devereux used a different modified equation based on narcolepsy findings of 34 patients, using the Penn Conversion as the border definition criteria (82):

$$\textbf{LV Mass (Penn)} = 1.04\,((\text{LVIDD} + \text{PWTD} + \text{IVSD})^3 - (\text{LVIDD})^3) - 13.6\text{g}.$$

DEVEREUX FORMULA 2:

Devereux then proposed a new adjusted equation, validated on necropsy findings of 52 individuals, using the ASE convention on border definition (83):

$$\textbf{LV Mass (ASE)} = 0.8(1.04\,((\text{LVIDD} + \text{PWTD} + \text{IVSD})^3 - (\text{LVIDD})^3)) + 0.6\text{g}$$

The American and European Societies of Echocardiography both recommend Devereux Formula 2 for estimation of LV mass as it is validated by necropsy ($r = 0.90, P < 0.001$) (17).

This is the reason I have used this formula to calculate LV mass in this study and I have excluded patients with LV systolic dysfunction as this formula is appropriate for evaluating patients without major distortions of LV geometry (e.g. patients with previous myocardial infarctions and poor LV systolic function).

1.3.5 Indexing for the Patients Body Size

Both body size and body habitus are associated with LV dimensions and mass. Several indices for body size correlation have been proposed such as height, body surface area and body mass index. Different criteria for body size adjustment and their cut off values result in different prevalence of LVH in population studies. The body surface area correction reduces variability due to body size and gender, but this index underestimates LV mass in overweight and obese individuals (84, 85). The ability to detect LV hypertrophy related to obesity is enhanced by indexing LV mass for the power of its growth relation with height (height $^{2.7}$). This is derived from regression models in normal samples from De Simone and appears to offer the most accurate estimation of LV hypertrophy particularly in obese individuals (86). Other studies have found LVH indexed to Height $^{2.7}$ to be a better predictor of cardiovascular events than LVH indexed using body surface area (87-89).

1.3.6 Determining Reference Values for LVH

LV mass, as with most biological variables, are in a Gaussian distribution. The determination of abnormal values is a source of controversy that includes differences in LVH formulas, sex, ethnicity, body size etc as explained previously. In this study LVH was defined as LV mass index greater than 110g/m^2 for females and 134g/m^2 for males using standard criteria (85). LV mass indexed to $Height^{2.7}$ greater than 50g/$m^{2.7}$ in males and greater than 47g/$m^{2.7}$ in females was defined as LVH. These represent the upper limits of the normal sex-specific 95% confidence intervals (CIs) of a reference population of 137 men and 91 women aged 18 to 73 years (84, 86).

1.3.7 Geometric Patterns of LVH

Calculation of Relative Wall Thickness (RWT) by the formula:

$$\frac{2 \times PWTD}{LVIDD}$$

permits categorization of an increase in LV mass as either concentric (RWT>0.45) or eccentric (RWT<0.45) hypertrophy and allows identification of concentric remodeling (normal LV mass with increased RWT).

Numerous studies have established that the left ventricle adapts to stress, such as hypertension, by developing a variety of geometric patterns of which four have been defined (**Figure 1.2**):

1. Normal geometry (Normal LVMI & RWT)
2. Concentric remodeling (Normal LVMI & Increased RWT)
3. Eccentric LVH (Increased LVMI & Normal RWT)
4. Concentric LVH (Increased LVMI & RWT).

The traditional hypertensive pattern of concentric LVH has been observed in only a minority (6%-24%) of asymptomatic hypertensive patients in most studies (90-95). In these studies a larger proportion of hypertensive patients had, eccentric LVH, concentric remodeling, or normal LV geometry than concentric LVH. In a prospectively planned echocardiographic sub-study involving 960 patients of the Losartan Intervention For Endpoint reduction in Hypertension (LIFE) study, **45.6%** of patients had Eccentric Hypertrophy compared to **23.9%** who had Concentric Hypertrophy, **19.1%** who had normal geometry and **10.5%** who had Concentric Remodeling (91). The average age of this population was 65 years with just over half being male.

In one of the largest studies to date investigating the prevalence of LVH in the general population, Milani and colleagues assessed echocardiograms from 35,602 participants from a clinical echocardiographic database in New Orleans (96). These participants had no evidence of aortic stenosis and had a normal left ventricular ejection fraction. The average age of this population

was 60 years and 47% were male. There was no information in the paper about the prevalence of hypertension in this group. The most common pattern was of normal geometry (**54%**) followed by concentric remodeling (**35%**), concentric hypertrophy (**6%**) and eccentric hypertrophy (**5%**).

Krumholz and colleagues studied the echocardiographic pattern of LV remodeling in 3,216 participants of the Framingham population who had adequate quality echocardiograms and found different relative prevalences to that of Milani, despite both populations being similar (97). The average age of the Framingham cohort was 55years for male and 57 years for female subjects with 43.5% of the population being male. In this population 76% of males and 72% of females had normal geometry followed by 8% of males and 12% of females having eccentric hypertrophy. There were 8% of males and females with concentric remodeling and concentric hypertrophy. The main difference in the two groups was that there was more concentric remodeling in Milanis paper and more normal geometry in the Framingham population. The prevalence of concentric hypertrophy and eccentric hypertrophy were similar in both groups of between 5% and 8%. Of this cohort; 23% of females and 18% of males were taking antihypertensive medication.

Therefore, in a general population, the majority of people have normal geometry and the three patterns of abnormal geometry are equally distributed.

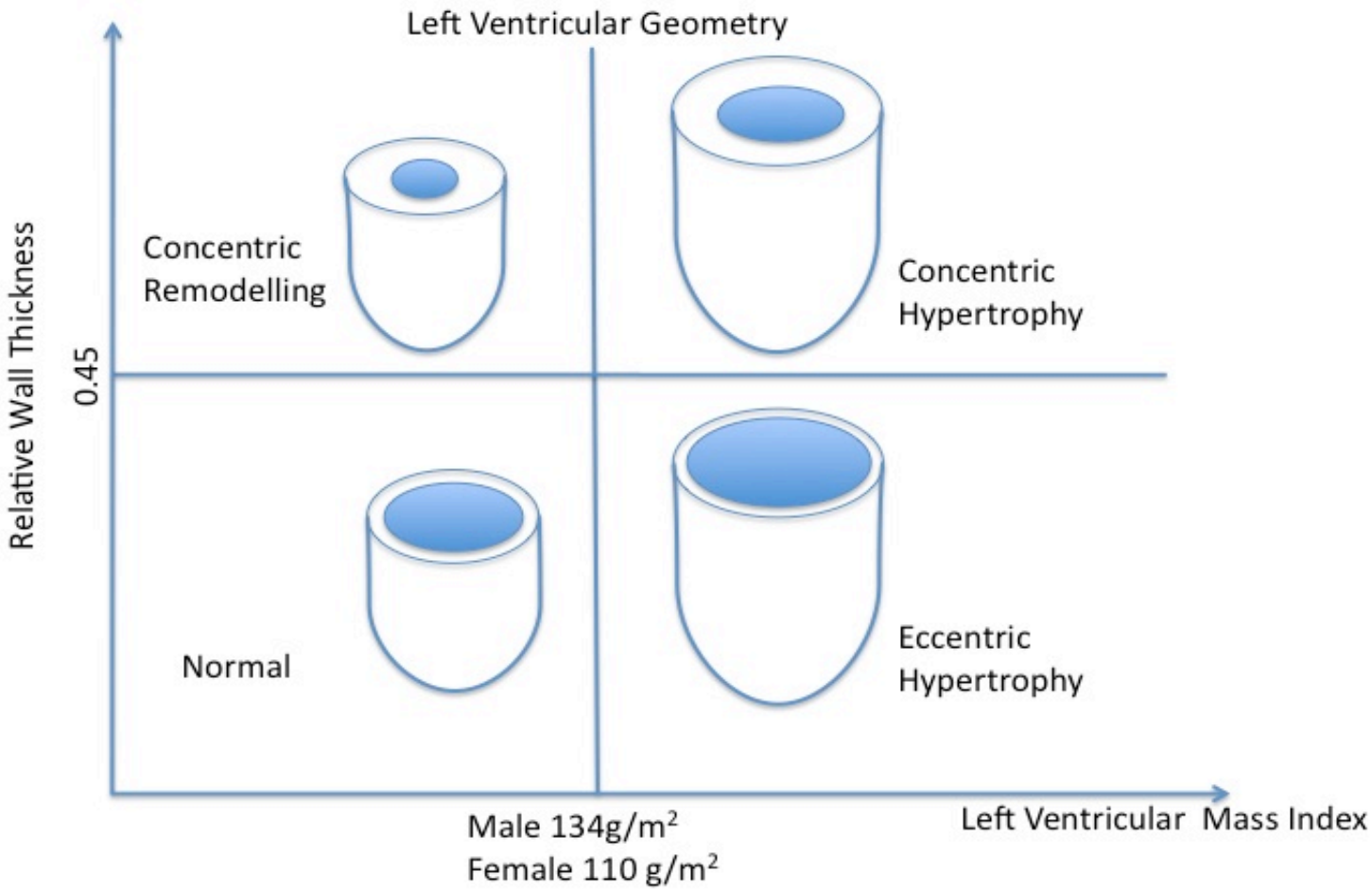


Figure 1.2 Patterns of LV geometry defined by LVMI and Relative Wall Thickness

In a large cohort study of 988 patients undergoing coronary angiography for investigation of coronary artery disease, there was a very large prevalence of **concentric hypertrophy** in those with (25%) and without (30%) coronary artery disease (98). Of those without coronary artery disease 25% had **normal geometry**, 33% had **concentric remodeling** and 17% had **eccentric hypertrophy**. In patients with confirmed coronary artery disease (at least one artery with >70% narrowing) 31% had **normal geometry**, 19% had **concentric remodeling** and 20% had **eccentric hypertrophy**. The average age of this population was 55 years with 36% of those without coronary artery disease and 55% with coronary artery disease being male. There was 83% prevalence of hypertension in both groups.

In a study of 165 patients with untreated hypertension, abnormal LV geometry was found in 48%. This comprised 13% with **concentric remodeling**, 27% with **eccentric LVH**, and 8% with **concentric LVH** (90). In another series of 271 untreated hypertensive patients, abnormal LV geometry was found in 35%, including 20% with **concentric remodeling**, 9% with **eccentric LVH**, and 6% with **concentric LVH** (94). Therefore, in a population of patients with hypertension, abnormal geometry is very prevalent, generally more than 30% of patients. The distribution of geometry is heterogeneous in this group in the different studies.

In a case control study involving patients with first diagnosed stroke and age, sex and ethnic race matched controls; Di Tullio and colleagues examined the prevalence of abnormal LV geometry and prognosis (99). Stroke patients had

a significantly higher proportion of **concentric hypertrophy** (13% versus 6%) and **eccentric hypertrophy** (33% versus 20%) than controls. Normal LV pattern was significantly more frequent in controls compared to stroke patients (65% versus 43%). There was no statistical difference in amount of concentric remodeling between the groups, with 11% in stroke patients and 9% in controls. Patients who have suffered ischaemic strokes have similar prevalence of LVH to that of patients with hypertension.

1.4 BLOOD PRESSURE AND LEFT VENTRICULAR HYPERTROPHY

There is an important misconception that patients with LVH are always hypertensive. In Framingham, LVH occurred in 28% of women over 60 years with a systolic blood pressure within the normal range (BP 125-139mmHg) (10). The Strong Heart study looked at the relationship of echocardiographically determined LV mass to demographic variables, blood pressure and cardiac function in 1,935 Native American Indians. This large study showed that half of the variability in LV mass was unexplained. Of the proportion that could be explained, there were six independent predictors of LV mass; and systolic blood pressure was only the third most important (100). In a study of diabetic patients in Ninewells Hospital, Dundee, blood pressure could not accurately identify those patients that had LVH. Twenty Six percent (26%) of diabetics who had normotensive office blood pressures, on or off antihypertensive medication (SBP<140mmHg) had echocardiographic LVH (101). In 7,924 adults in the second National Health and Nutrition Examination Survey (NHANES II) population there was evidence of LVH in 6.4% of those without hypertension (8).

The lack of correlation between blood pressure and LVH seen in these studies is likely to be mirrored by my population of PAD patients in this study. The important point here is that the prevailing level of blood pressure is in general, a poor predictor of the presence of LVH and probably an even poorer predictor in PAD patients. This will be investigated in my study.

The existence of ‘normotensive’ LVH does illustrate that all cut-offs are artificial to some extent and that all parameters are really in a continuous distribution. In clinical practice, so-called "normotensive" patients with LVH exist and they deserve better control of their risk factors. In routine clinical practice, doctors act more in response to cut-offs and targets than respond to continuous distributions; this is understandable but potentially puts patients at danger if risk factors are not modified. Another related issue is that normotensive LVH patients are probably a heterogeneous group, which includes normotensive LVH individuals with BPs in the upper normal range and whose "normal BPs" should perhaps be reclassified as high. There are also groups of patients with normal clinic blood pressure but hypertensive out of the office setting, or those patients whose blood pressure does not follow the circadian rhythm and drop overnight. There are a proportion of hypertensive patients whose LV masses have not regressed into the normal range but whose BPs have fallen into the normal range, who also may benefit from more intensive risk factor modification. Indeed, in a study of 2,051 people in a general Italian population aged 25 to 74years, 20% of successfully treated hypertensive individuals using 24 hour Blood Pressure monitoring and 5% of normotensive individuals had LVH (102). In this large population study LVH was more common in patients with poorly controlled hypertension (33%) compared to those that had good blood pressure control (20%) suggesting regression of LVH with good anti-hypertensive treatment.

What is clear is that hypertension is a risk factor for LVH but not everyone with hypertension develops LVH and conversely not everyone with LVH has hypertension. There is a significant population with normal blood pressure but have LVH evident and are at risk of complications from this. This study will shed light on the association of blood pressure and LVH in a population of patients with newly diagnosed PAD.

1.5 PROGNOSIS AND LEFT VENTRICULAR HYPERTROPHY

It is well established that LVH determined by ECG, Echocardiography or MRI is a powerful risk factor for cardiovascular morbidity and mortality with relative risks of between **1.5** to **4.0** for cardiovascular morbidity and between **1.5** and **8.0** for all-cause mortality (8, 9, 11-13, 15, 88, 89, 91, 95, 97, 99, 103-121). Starting as an adaptive mechanism to compensate for increased cardiac workload, LVH can contribute to increased rates of cardiovascular events through its deleterious effects on ventricular function, coronary circulation, and arrhythmogenesis. The prevalence of LVH is dictated somewhat by age, increasing from 6% in Framingham subjects under age 30 years to 43% in those aged 70 years or older, this remains true even after multivariate analysis (10). LVH prevalence also varies with severity of hypertension, ranging from less than 10% in people with normal blood pressure to >40% in patients with hypertension (8, 10, 33, 67, 90, 92, 100, 102, 118, 122-136). After adjustment for confounding factors left ventricular hypertrophy remains an important independent risk factor for morbidity and mortality.

1.5.1 LVH and Cardiovascular Morbidity

1.5.1.1 Electrocardiographic LVH and Morbidity

The difficulty interpreting studies using ECG LVH criteria is that they vary between studies and include the Perugia score, the Minnesota Code, voltage

criteria (Sokolow-Lyon index, Cornell voltage, Romhilt-Estes point score) and other study-specific criteria using QRS voltage, ST segment, and T-wave changes. Studies using ECG criteria reveal that LVH is associated with a **1.6-** to **4.0**-fold higher risk of future cardiovascular morbid events (114, 137-146). The populations in these studies were heterogeneous and included those with acute myocardial infarction, hypertension, elderly subjects (over the age of 70 years), and the Framingham population. Most studies had a predominantly male population. LVH was more prevalent in male compared to female patients. The prevalence of ECG LVH ranged from **6%** to **35%** with the lowest prevalence in the Framingham group and the highest in male patients in an outpatient hypertension clinic using the Sokolow-Lyon criteria (139). Follow-up times in these studies ranged from 1 to 10 years. In most of these studies LVH was associated with increased cardiovascular morbidity in the form of myocardial infarction, angina, stroke, transient ischaemic attack, symptomatic aorto-illiac occlusive disease, peripheral thromboembolism and congestive cardiac failure even after multivariate analysis. Echocardiography is more sensitive and specific for diagnosing LVH and so I have presented only limited data on ECG diagnosis of LVH and concentrated on presenting data in the next section on Echo LVH.

1.5.1.2 Echocardiographic LVH and Morbidity

The prevalence of LVH using echocardiographic criteria varies in all studies due to differing LVH criteria and, similar to those studies using ECG criteria, different heterogeneous population studied; but ranges from **10%** to over **70%** (7, 11, 12, 16, 89, 91-93, 95, 97, 99, 103, 104, 106, 107, 110, 115, 116, 122, 124, 126, 147-152). The majority of these studies were on Caucasian populations with hypertension or recent history of myocardial infarction. Other groups studied were dialysis patients, elderly patients, Afro-American populations, the Framingham population, inner city hospital populations, the LIFE Study population and patients presenting with first stroke. All these studies demonstrate that LVH is exceedingly common in different populations of patients with cardiovascular risk factors and disease.

These studies also reveal that LVH is consistently and powerfully associated with cardiovascular morbidity with a **1.5** to **3.5** fold higher risk of future cardiovascular morbid events even after adjustment for cardiovascular risk factors such as age, sex, cardiovascular disease, cholesterol, smoking, hypertension, diabetes, BMI and LV systolic function. End points defining cardiovascular disease varied among studies but included cerebrovascular thrombotic events (stroke or TIA), myocardial infarction, heart failure and angina. LV mass was indexed to body surface area or height with different

cutoff values for LVMI in each study. Follow-up periods in these studies ranged from 1 to 10 years.

Even in a relatively low risk group of individuals LVH is a powerful independent prognosticator for future cardiovascular morbidity. In one of the largest studies to date looking at the prognostic implications of LVH, Levy and colleagues demonstrated a relative risk of cardiovascular disease (in the form of coronary heart disease, congestive heart failure, stroke or TIA and intermittent claudication) of **1.49** for each increment of 50g per metre in LV mass corrected for height in men and a relative risk of **1.57** in women (11). These relative risks were based on multivariate analyses correcting for age, diastolic blood pressure, pulse pressure, antihypertensive treatment, cholesterol, smoking, diabetes, BMI and ECG evidence of LVH. This was during a 4-year follow-up of 3,220 subjects enrolled in the Framingham Heart Study who were free of clinically apparent cardiovascular disease and had echocardiographically determined LV mass. 43.5% of this population were male and the average age was 54.5 years for males and 56.9 years for females. **15.5%** of males and **21%** of females in this cohort had echocardiographically determined LVH. So, even in a low risk general population LVH is seen to be very prevalent and an important pointer to future cardiovascular events. In my PAD population, I expect the prevalence of LVH to be higher and therefore a very important and potentially reversible prognostic marker.

Another study with a relatively low risk population demonstrated a similar risk

of stroke in people with LVH compared to those without. The study population consisted of 1,792 participants of the Atherosclerosis Risk in Communities (ARIC) study which was a prospective, population based investigation in the United States (147). The unadjusted relative risk of ischaemic stroke was **1.36** for every $10g/m^{2.7}$ increment. In a multivariate analysis adjusting for age, sex, hypertension, systolic blood pressure, smoking diabetes mellitus, cholesterol, BMI, coronary artery disease, congestive heart failure, left ventricular ejection fraction and left atrial size the relative risk was **1.17**. The average age of this population was 58.8 years with 35.7% men. In this mainly African American cohort with a median follow up of 8.8 years there was a high prevalence of LVH in those who developed a stroke (**62.2%**) compared to those with no stroke (**38.6%**) (147). It is important to point out that in this population based study; LVH was a significant independent predictor of ischaemic stroke, even taking into account traditional risk factors.

In a population based case-control study comparing 394 mostly Hispanic patients with first ischaemic stroke with 413 age, sex and ethnic race matched, stroke free controls, LVH was associated with a **2.5** fold increase in stroke risk after adjustment for other risk factors (99). Concentric LVH carried the greatest stroke risk with a relative risk of **3.5**. The average age of this population was 68 years with 46% males, 17.2% white, 28.2% black and 54.6% Hispanic. Few studies are available on a mixed race population, especially representing the Hispanic community. This study demonstrated that

LVH was independently associated with the risk of stroke in all ethnic groups with an adjusted odds ratio of **4.6** for whites, **2.1** for blacks and **2.3** for Hispanic individuals.

The mechanism of ischaemic stroke is not clear. LVH may cause cerebrovascular events due to its relation to left atrial enlargement and atrial fibrillation; which are known risk factors for stroke and TIA (153-156). . This will be discussed in a future section of this thesis.

1.5.1.3 Summary of LVH and Cardiovascular Morbidity

There is a strong and reliable relationship between the presence of either ECG or Echocardiographic LVH and cardiovascular morbidity in the form of angina, myocardial infarction, stroke, transient ischaemic attacks, peripheral embolism, symptomatic aorto-iliac disease and heart failure. The overall weighted adjusted relative risk of cardiovascular morbidity in ECG and echocardiographic LVH studies combined is approximately **2.0**. This is true for all ethnic races studied.

1.5.2 LVH AND MORTALITY

1.5.2.1 Electrocardiographic LVH and Mortality

ECG is the first line method for assessing for LVH due to its availability, cost and ease of use. In a recent review of 26 studies investigating the utility of ECG LVH as a prognostic marker for mortality the prevalence of ECG LVH varied from **0.6% to 40%**, with an average prevalence of 18% in the pooled population (157). This extensive review included 40,444 individuals with hypertension and LVH was defined by 15 different criteria, demonstrating the heterogeneous nature of defining ECG LVH. Vakili published a review of ten studies evaluating a total of 38,262 individuals from diverse populations with cardiovascular risk factors or disease, and demonstrated the risk of all-cause mortality was **1.5- to 6.8** fold higher among those with ECG evidence of LVH at baseline (12). Mean age was greater than 48 years with the prevalence of LVH ranging from **1%**, in patients undergoing angiography to **44%** in patients with hypertension. The ECG LVH criteria varied between studies and included the Romhilt-Estes, Minnesota Code, and other study-specific criteria using QRS voltage, ST segment, and T-wave changes. Mean follow-ups were between 4 years to 10 years. The highest RR **(6.8)** was observed among patients with LVH seen in the emergency department with angina; however, this figure was not adjusted for other risk factors. In the two studies reporting outcomes by sex, LVH conferred a higher risk in women in one study (141) and a slightly lower risk in another (139), compared with men (**2.4 vs 2.0** and

2.1 vs 2.2, respectively). ECG evidence of LVH is a useful and powerful test for risk stratification regardless of the patient population or ECG criteria used. Each ECG criteria has its own sensitivity and specificity, which is inferior to that of echocardiography. These are the reasons I have concentrated on echocardiographically assessed LVH in my study.

1.5.2.2 Echocardiographic LVH and Mortality

The prevalence of Echocardiographically determined LVH in studies looking at mortality, as with morbidity, varies substantially depending on the criteria used and the population studied. In a review of 30 studies, including 37,700 untreated and treated hypertensive patients, prevalence varies from **10%** up to **77%** (158). Eccentric LVH was more frequent than concentric LVH (**20.3%** versus **14.8%** respectively). As with ECG diagnosis of LVH, the studies using echocardiography are also heterogeneous with 23 different criteria being used. This emphasizes the fact that there is weak consensus about the most accurate method and values used to assess the presence of LVH and different formulas used in different populations of subjects. This limits somewhat the accurate assessment of risk of LVH in defined populations. Nevertheless, there is no doubt that LVH is prevalent is prognostically devastating.

In a review of seven heterogeneous prospective studies evaluating a total of 5,478 patients, the relative risk for all-cause mortality associated with baseline LVH ranged from **1.0 to 8.0** (12). These studies included low risk patients such

as the Framingham population and high-risk populations, such as those with end stage renal disease, diabetes, ischaemic heart disease and hypertension. The prevalence of LVH ranged from **16%** among Framingham men to **74%** in patients with end-stage renal disease (11, 159). Follow-up ranged from 2 to 12 years, mean age was greater than 50 years and the majority of patients were men.

LVM indexed for body surface area was used in most studies to define LVH; however, one study used LVM indexed for height and another used a combination of wall thickness and ejection fraction (11).

All studies except one, reported outcomes after adjustment for baseline risk characteristics. Studies that reported end points by sex found a higher RR in women (**2.0 to 4.3**) with baseline LVH than their male counterparts (**1.5 to 2.0**). The one study that did not find any increased risk associated with baseline LVH was conducted in patients with end-stage renal disease, 79% of whom had CAD, peripheral arterial disease, or arrhythmia and had an overall median survival of 50 months (159). This is likely to be because this population has a very poor prognosis anyway because of severe concomitant cardiovascular disease and the presence of LVH in this group has minimal extra effect.

1.5.2.3 Summary of LVH and Mortality

There is a consistently powerful relationship between the presence of either ECG or Echocardiographic LVH and all-cause mortality. Excluding the study of high risk dialysis patients (159), the overall weighted adjusted RR of all-cause mortality associated with LVH, in ECG and echocardiographic LVH studies combined, was **2.5** in the review by Vakili and colleagues (12). The mean overall risk of cardiovascular morbidity, in the form of angina, MI, stroke, peripheral arterial disease in this study is **2.3**.

The overall risk of morbid or mortal events is roughly similar for ECG and Echo LVH but echocardiography has a better sensitivity and specificity at diagnosing this condition. The prevalence of baseline LVH in studies using echocardiography was between **16%** and **74%,** compared to between **1%** and **44%** in studies using ECG criteria(12). In this paper they estimate that, if the prevalence of LVH was **20%** in a population and the adjusted **RR** is **2.0**, then almost **20%** of cardiovascular events would be associated with LVH.

Left ventricular hypertrophy has not been studied in patients with peripheral arterial disease but is likely to be far more prevalent than **20%,** given its risk factors and therefore confer a significant risk of cardiovascular morbidity and mortality.

1.5.3 LVH GEOMETRY AND PROGNOSIS

We have seen that LVH is prevalent in many populations, especially those with cardiovascular risk factors or disease and is a significant risk factor for morbidity and mortality. Geometric LV pattern may also be important and contain additional prognostic information.

In a study of 988 consecutive patients undergoing coronary catheterization, the risk of all-cause mortality per 100 patient-years for patients with normal, concentric remodeling, eccentric and concentric LVH was **1.5%, 1.7%, 2.8%, and 4.2%** respectively, in patients without coronary disease. Mean follow-up was 9 years. In patients with proven coronary artery disease the risk was almost doubled at **2.7%, 3.6%, 5.4%, and 7.6%** respectively (**Figure 1.3**) (110). In this cohort, concentric LVH conferred a significantly increased relative risk of all cause mortality (**2.21**) and cardiovascular mortality (**2.97**). Eccentric LVH conferred a moderate risk of all cause mortality and significant risk of cardiovascular mortality (**RR 1.33 and 2.87** respectively) (98).

In an observational study of 280 patients with essential hypertension and no prior cardiac disease, the 10-year incidence of cardiovascular events and death was worst in patients with concentric hypertrophy (**31%, 21%**) compared to those with eccentric hypertrophy (**23%, 10%**), concentric remodeling (**15%, 3%**) and normal geometry (**11%, 0%**) (92). Verdecchia and colleagues demonstrated in a study of 694 hypertensive patients with **normal LV mass** (<125g/m^2) the risk of cardiovascular events was statistically higher in the group with concentric remodeling compared to the

patients with normal geometry (**relative risk 2.56**) over a mean follow-up of 7.7 years (116).

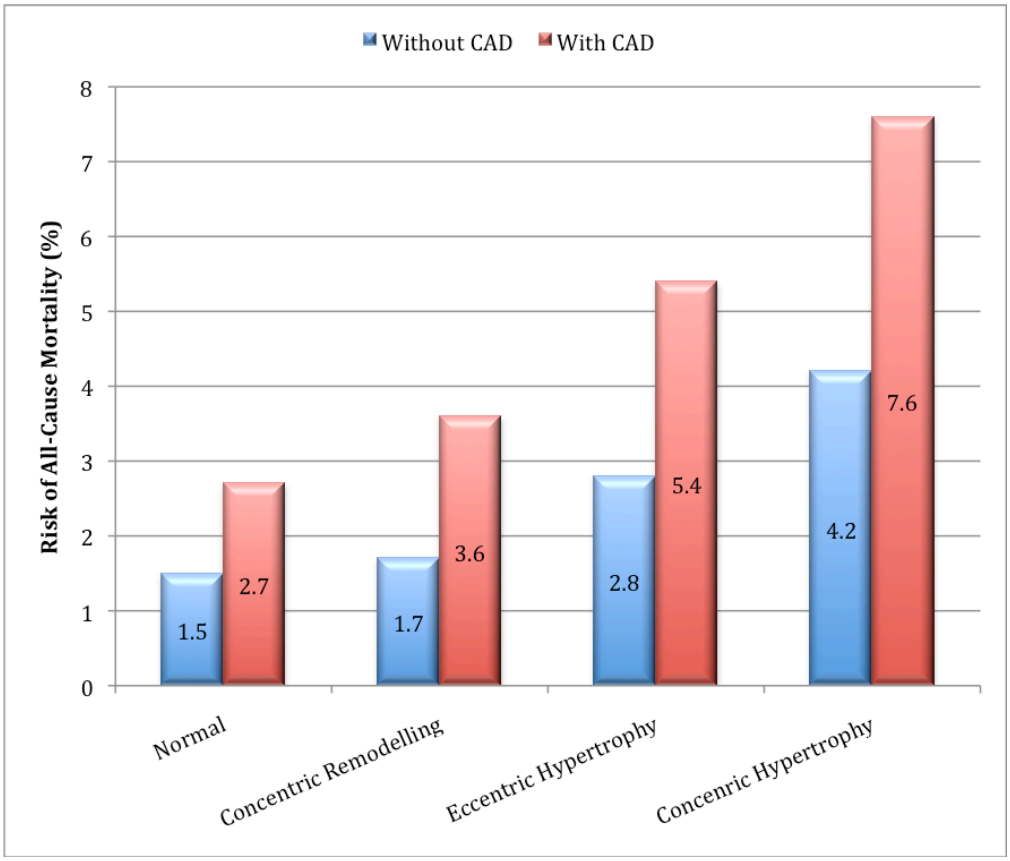


Figure 1.3 Risk of All Cause Mortality in Patients with and without Coronary Artery Disease (CAD) in patients undergoing coronary catheterization. *Data from Ghali et al (1998)* (98)

Data from the Framingham Heart Study using 3,209 patients, who were ≥40 years old and free from cardiovascular disease with adequate follow up and good quality echocardiogram, showed that the cardiovascular event rates in men and women were highest in the concentric hypertrophy group and lowest on the normal geometry group. This was even after adjustment for traditional cardiovascular risk factors (97). This study showed a relative risk of **2.1** for all cause mortality in men and a RR of **1.6** in women with concentric hypertrophy (97). This study demonstrated that subjects with concentric hypertrophy had the worst prognosis followed by those with eccentric hypertrophy, concentric remodeling and normal geometry. It is important to emphasize that this was in a population who were free of cardiovascular disease at baseline.

Taken together, these studies illustrate that LV geometry stratifies risk of adverse outcomes and is independent of BP and other conventional risk factors. More recently, LV geometry was also demonstrated as a predictor of cardiovascular risk during antihypertensive drug therapy in the LIFE Echocardiography Sub-study (91). Out of the 9,193 patients in the parent LIFE Study, 960 subjects were prospectively assessed with annual echocardiographic follow-up. Among the 960 patients, analysis was undertaken in the 937 patients with measurable LV dimensions on the baseline echocardiogram. The study demonstrated at baseline that among hypertensive patients with ECG signs of LVH, the most common LV geometry was **eccentric LVH** (47%), followed by **concentric LVH** (24%),

normal (19%) and **concentric remodelling** (10%). However, LV geometry changed significantly during follow-up as a result of aggressive antihypertensive treatment. By the end of the follow-up period of 4.8 years, the proportions with each of these LV geometries were **30%, 5%, 63%, and 3%**, respectively (P< 0.001). Baseline LV geometry did not predict outcome in the LIFE substudy but in multivariate Cox regression analysis, each abnormal LV pattern after treatment independently predicted risk of the composite endpoint compared with normal LV geometry (P<0.05) (**Figure 1.4**).

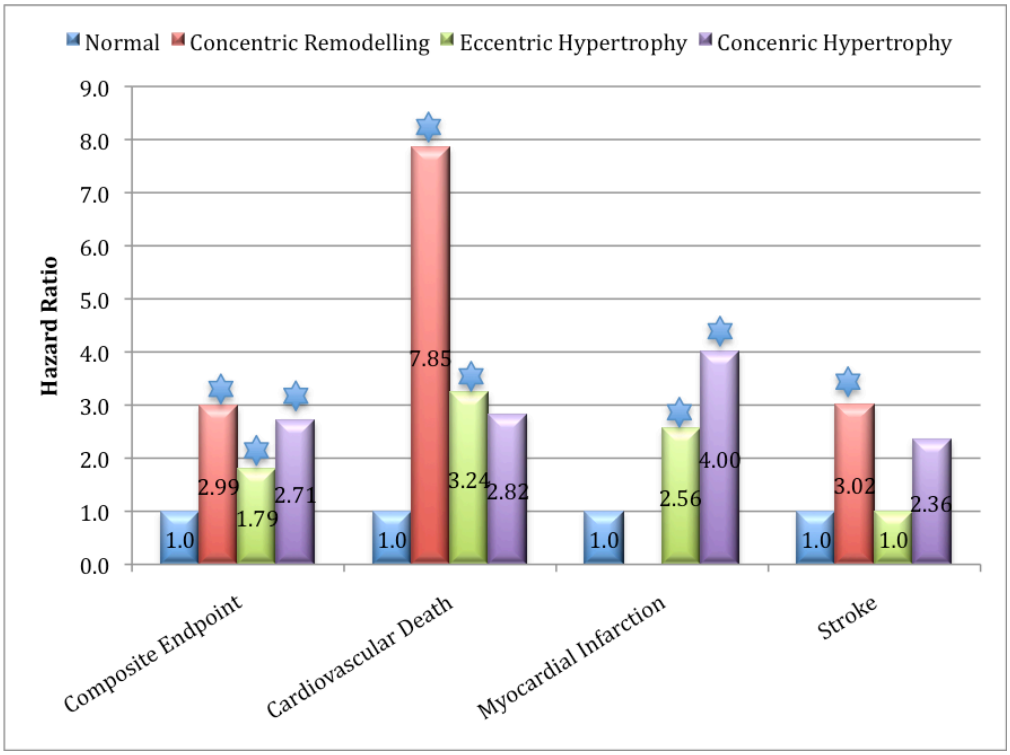


Figure 1.4 Influence of LV Geometry on Cardiovascular Risk after Treatment in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Echocardiography Study. P<0.05

No patients with concentric remodeling at final study experienced myocardial infarction

Modified from Gerdts et al 2008 (91)

When the individual components of the composite endpoint were considered separately in similar multivariate models:

> **Concentric remodeling** was associated with increased risk of cardiovascular death (**HR 7.85**) and stroke (**HR 3.02**),
>
> **Eccentric hypertrophy** with increased risk of cardiovascular death (**HR 3.24**) and MI (**HR 2.56**), and
>
> **Concentric hypertrophy** with increased risk of MI (**HR 4**).

This analysis demonstrates that evaluation of LV geometry after treatment adds prognostic information to clinical evaluation and assessment of LVH in patients with hypertension, with concentric remodeling showing the highest risk of cardiovascular death.

A population based case-control study with 394 patients with first ischemic stroke and 413 age, sex and ethnically matched controls demonstrated concentric hypertrophy carried the greatest stroke risk with an adjusted OR of **3.5**. This was followed by eccentric hypertrophy (**OR 2.4**) and concentric remodeling (**OR 1.7**) (99). This is in contrast to the LIFE substudy population.

Analysis using 5,888 participants of the Cardiovascular Health Study (CHS), which is a longitudinal, multicenter cohort study of elderly men and women (>65 years old) found that eccentric and concentric LVH increased the risk of heart failure (Adjusted HR **2.95** and **3.32** respectively) and coronary heart

disease (Adjusted **HR 2.02** and **1.61** respectively) (109). No LV geometric pattern increased the risk of stroke in this elderly general population.

Additional data will be needed to determine whether the adverse implications of specific LV geometric patterns are consistent across populations and remain significant in analyses adjusting for co-variates. Overall, it appears that concentric hypertrophy consistently confers the worst prognosis in most of the studies with information on geometric patterns. In the LIFE substudy by Gerdts and colleagues, concentric remodeling conferred the worst prognosis in terms of cardiovascular death (91). A possible explanation for this is that this abnormal geometric pattern is more difficult to reverse with pharmacological therapy, thereby increasing the risk. In comparison, concentric hypertrophy regresses more easily with anti-hypertensive therapy and therefore may improve prognosis. I will discuss this in more detail in the later section on LVH regression.

1.5.4 PROGNOSIS AND LVH SUMMARY

The relationship between the presence of either ECG or Echocardiographic LVH and subsequent cardiovascular and all-cause mortality is impressively strong. This is consistent for all populations studied.

Women with LVH appear to be at equal, if not higher risk, of adverse outcomes compared to their male counterparts. The average weight adjusted RR of cardiovascular morbidity is **2.0** for females versus **2.4** for males. With a RR of all-cause mortality being **2.3** for females versus **1.9** for males.

On a population basis, the clinical significance of the association between LVH and cardiovascular events depends, in part, on the prevalence of LVH. The prevalence of baseline LVH is higher in studies using anatomically validated echocardiographic methods than in studies using electrocardiographic criteria (**16%-74%** vs **1%-44%**, respectively). This suggests that the population burden of cardiovascular events associated with LVH is extremely considerable. For instance, with a population prevalence of LVH of **20%** and an adjusted relative risk of **2.0**, almost **20%** of cardiovascular events would be associated with LVH (12). If LVH is more prevalent than **20%** in PAD patients then the amount of cardiovascular events is likely to be even higher in this group.

One of the most comprehensive studies looking at adverse cardiovascular outcomes was that of *Liao et al* (1995). In addition to standard adjusted risk calculations, LVH was shown to have an even worse outcome (**RR 2.4**) when

compared to multivessel coronary artery disease (**RR 2.0**) and reduced ejection fraction (**RR 1.6**) (7). All these data suggested that LVH is likely to be far more prevalent in PAD patients and the morbidity and mortality burden of LVH is expected to be considerable.

1.5.5 CONSEQUENCES OF LVH

It has been consistently shown that LVH is strongly associated with the risk of cardiovascular morbidity, in the form of stroke, MI, heart failure, arrhythmia and angina. It is also strongly associated with all cause and cardiovascular mortality. It starts off as a compensatory mechanism and then becomes a powerful and independent risk factor for morbidity and mortality. In this section we will discuss the possible physiological reasons for these consequences.

1.5.5.1 LVH, Atrial Fibrillation and Stroke

The mechanism of ischaemic stroke is not clear but LVH may predispose individuals due to its relation to left atrial enlargement. Left atrial dilatation is a known risk factor for thromoembolism (153-156). A separate mechanism is that both left atrial dilatation and LVH are risk factors for atrial fibrillation (AF). Atrial fibrillation is the most common arrhythmia in the general population and its prevalence increases with age (160-162). AF, itself, is a strong risk factor for ischaemic stoke, primarily because it causes left atrial appendage thrombus formation (154, 155, 163-167). The mechanisms underlying the increased thrombogenic risk of AF are complex and remain

only partially elucidated. In the Framingham population, AF increased the risk of stroke by almost five fold (168). Suggested mechanisms of the increased stroke risk include stasis, procoaguable state with platelet and clotting factor abnormalities and endothelial dysfunction and inflammation (164). Abnormalities in the Renin-Angiotensin-Aldosterone-System (RAAS) are important in numerous cardiovascular diseases. Atrial tissue has the ability to produce these hormones, primarily Angiotensin II, which is up regulated in AF (169, 170). Angiotensin II is proinflammatory, pro-apoptotic and pro-thrombotic. Modulation of the RAAS with either ACE-inhibitors, Angiotensin Receptor blockers or Aldosteone has been proven to be prognostically beneficial in a number of diseases including hypertension, LVH and heart failure. Importantly, one can reduce the incidence of atrial fibrillation and decrease left atrial size by treating hypertension with commonly prescribed medication such as angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) (166, 167).

Various substudies of the LIFE study have demonstrated a strong relationship between LVH and left atrial size and new onset AF. In 941 participants of the LIFE echo substudy (mean age 66 years), left atrial diameter was measured at baseline (171). Enlarged left atrial diameter was present in 56% of women and 38% of men and was strongly associated with LVH (**OR 2.46**) and AF (**7.18**) (171). In logistic regression analysis, LA enlargement was related to LVH and in particular eccentric geometry. This is surprising, as it appears from previous LIFE studies that concentric hypertrophy carries the strongest risk for cerebrovascular events and not eccentric hypertrophy (171).

In various LIFE substudies the use of the angiotensin receptor blocker Losartan significantly reduces the incidence of AF by 33% and reduced stroke by an impressive 55% (163, 167, 171-174). Losartan reduced left atrial diameter by 19mm compared to just 6mm in the Atenolol arm (174). This was despite similar reductions in blood pressure between the two treatment groups (Atenolol versus Losartan). Thus, RAAS modulation has beneficial effects on both atrial fibrillation and stroke reduction in patients with LVH, perhaps by its beneficial effect on LA size.

1.5.5.2 LVH, Coronary Flow Reserve and Ventricular Arrhythmias

A study from the Framingham population demonstrated that LVH was associated with a relative risk of sudden cardiac death of **1.53** over a 14-year follow-up period (148). Importantly, regression of LVH in the LIFE study, during a mean follow-up period of 4.8 years was associated with a significant reduction in sudden cardiac death (**HR 0.7**) (175). Sudden cardiac death is likely related to increased ventricular arrhythmias in LVH patients. The possible mechanisms by which LVH causes ventricular arrhythmia are not well understood and are numerous. Some mechanisms may be that LVH prolongs the action potential in cardiac myocytes and this predisposes them to early afterdopolarisations and increased triggered activity (176, 177). It also increases refractoriness within the LV and both these mechanisms have been

associated with increased risk of polymorphic ventricular tachycardia and ventricular fibrillation (176-180).

A hallmark of severe chronic LVH is fibrosis and collagen deposition (181-183). Fibrosis and collagen deposition is akin to scar, which is a potent risk factor for ventricular arrhythmia (184). LVH reduces coronary flow reserve and increases myocardial oxygen requirements (185, 186). Coronary flow reserve is a measure of the ability of the coronary vasculature to increase its blood flow to compensate for states of relative ischaemia. Coronary reserve has been defined as the ratio of coronary resistance under control conditions (rest) and of coronary resistance after maximal coronary vasodilatation (using vasodilatory drugs in the cardiac laboratory, such as dipyridamole). This imbalance may predispose to cardiac ischaemia, arrhythmia and sudden death (187-189). Structural and functional alterations of the coronary circulation have been reported in LVH. In people with LVH there is a lower ratio of subendocardial capillaries to LV mass and therefore when vascular growth does not match myocyte growth there is a reduction in coronary flow reserve. This picture is worsened if there is medial hypertrophy of the blood vessel wall giving rise to luminal narrowing and a further reduction in oxygen supply. The reduction in coronary flow reserve in hypertrophic hearts is caused by both a concomitant increase in resting myocardial blood flow, due to higher work load and oxygen consumption, and a reduction in hyperaemic response to endothelial dependant and independent stressors(190-193). Increased myocardial and extravascular compressive forces contribute mechanically to myocardial blood flow reduction in LVH. The subendocardium is underperfused during systole and it must therefore

compensate during diastole. Elevated end diastolic pressure in LVH can reduce subendocardial perfusion, particularly during physical or pharmacological stress, causing signs and symptoms of ischemia in the absence of significant epicardial coronary artery lesions (192). Moreover, the risk of ischemia is higher in dilated hearts (193).

Impaired coronary flow reserve is associated with both abnormal left ventricular relaxation and increased left ventricular filling pressure (194). Coronary flow reserve is negatively associated with LV mass (194). LVH and its effect on cardiac microcirculation and deleterious effect on the interstitium with increase in fibrosis can initiate and maintain a reduction in myocardial flow reserve. This is turn, can result in, not only depression of systolic function but also impairment of LV dispensability and increase in myocardial filling pressures (190, 191, 194, 195). In a substudy of The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, LVH was associated with impaired LV diastolic filling in a multiple regression model (195). A reduction in coronary flow reserve in patients with LVH initiates a process of reduced microvascular perfusion paralleling increased metabolic demand secondary to increased LV mass and pressure overload. The reduction in microvascular perfusion is also further reduced by the increased LV filling pressure and delay in LV relaxation found in patients with LVH (196). This is independent of levels of blood pressure. The beta-blocker, Nebivolol, improves LV filling pressure as well as coronary flow reserve (196).

There may also be asymptomatic coronary artery disease and narrowing in patients with LVH as they have similar risk factors. This will create more ischaemia and risk of arrhythmias and sudden death.

In a recent study of 317 patients with ischaemic cardiomyopathy (mean age 65 years) and implantable cardioverter defibrillators (ICD), ECG evidence of LVH was the only significant predictor of VT and VF in univariate analysis (105). In a multivariate analysis model it was a significant predictor of arrhythmia and death in this cohort. The unique advantage of this study is that they were able to detect arrhythmia easily due to the fact that the patients had an ICD and could therefore detect all significant arrhythmias. In another LIFE substudy of 1,326 subjects, Losartan significantly reduced the risk of sudden cardiac death compared to Atenolol with a HR of **0.49** (197). Losartan may have this beneficial effect by regressing LVH, reducing myocardial fibrosis and reducing cardiac arrhythmias.

In summary, LVH leads to worse outcome, in terms of morbidity and mortality, secondary to reduced coronary flow reserve, increased LV filling pressure, reduced systolic and diastolic LV function and increased risk of myocardial infarction, stroke, atrial fibrillation, ventricular arrhythmias and heart failure. Numerous studies, including the numerous LIFE sub-studies, have proven this. Importantly, regressing LVH, and especially using medications that target the RAAS can attenuate much of these events.

1.5.6 LIMITATIONS OF LVH STUDIES

ECG and echocardiographic criteria used to define LVH in published studies are not uniform and vary substantially. These differences have a potential impact on the prevalence of LVH, introducing a bias toward lower prevalence of LVH with more stringent ECG LVH criteria or higher LV Mass cutoff values for defining LVH and vice versa. Also, end points except all-cause mortality vary among studies. However, the risk of cardiovascular events associated with LVH is significantly increased irrespective of the prevalence of LVH or the end point used, suggesting that interstudy differences in LVH criteria or end point did not have a substantial effect on the overall evidence of a strong association between LVH and adverse outcomes. Taking all this into consideration, an important strength of most published studies is that they derived the estimates of risk in multivariate analyses that took potential confounding effects of conventional risk factors into account. This unequivocally confirms the strong association between LVH and adverse outcome.

Given the higher sensitivity of the echocardiogram for detecting LVH and the adverse prognostic implications associated with LVH, it would be desirable to reach a consensus with regard to a uniform definition of echocardiographic LVH. This would allow more direct comparison of studies and make possible pooling of such data in the form of a true meta-analysis. The classic indexation of LV mass for body surface area is useful for detecting

hypertension-associated LVH but tends to mask that associated with obesity. In contrast, indexation of LV mass to body height (height$^{2.7}$) appears to detect obesity-independent and obesity-related LVH equally well.

1.6 REGRESSION OF LEFT VENTRICUALR HYPERTROPHY

A fundamentally important issue with regard to the clinical significance of LVH is the degree to which LVH regression is associated with improvement in prognosis. Individuals in whom ECG or echocardiographic LVH regressed have significantly lower rates of subsequent cardiovascular events than those in whom LVH persisted or developed. LVH regression reduces events by up to 75% (12, 112, 114, 118, 123, 129, 175, 198, 199). *Verdecchia* and colleagues showed in a meta-analysis in 2003 that LVH regression lead to a significant reduction in cardiovascular events (**OR 0.41**)(200). A meta-analysis published 7 years later looking at the prognostic relevance of echocardiographically determined LVH regression in hypertensive patients confirmed that regression of LVH was associated with a significant reduction of cardiovascular events (118). In this rigorous analysis, only studies with multivariate analyses and adjusted hazard ratios, examining echocardiographic LVH regression and prognosis in hypertension were included. Five studies were identified, including a total of 3,149 patients with a follow-up of between 3 and 9 years. Overall, there was an adjusted **HR** of **0.54** for either LVH regression or persistent normal LV geometry versus LVH development or persistence. This contemporary meta-analysis demonstrates that LVH regression is associated with a significant improvement in cardiovascular outcome in patients with hypertension.

Important insights regarding the physiology of regression of hypertrophy in patients with hemodynamic overload can be drawn from a number of studies on patients before and after Aortic valve replacement and septal myectomy for patients with hypertrophic obstructive cardiomyopathy (201-203). Normalisation of systolic load through aortic valve replacement causes a rapid reduction in myocyte hypertrophy and LV mass (35% reduction) within a few weeks after valve replacement. In this early phase there is rapid regression of myocyte hypertrophy but little change in collagen and matrix. During continued reduction of load many months to a few years after valve replacement, regression of interstitial fibrosis and further regression of LVH occurs, resulting in near-normalisation of both muscle mass and fibrous tissue. In these studies, the increased biomechanical loads were abruptly reduced by mechanical valve replacement in the absence of pharmacological interventions.

Dahlof and colleagues performed a meta-analysis of 109 studies involving 2357 hypertensive patients on the effects of antihypertensive treatment on LVH (204). In this analysis, ACE inhibitors reduced LV mass by **15%.** Lesser reductions were achieved with diuretics (**11**%), ß-blockers (**8**%), and calcium-channel blockers (**8.5%**). Overall, LV mass was reduced by **11.9%**, which is less than the magnitude of regression observed after valve replacement.

The lower magnitude of regression observed in pharmacological trials in hypertensive patients is likely related to an incomplete reduction of hypertension itself. Nevertheless, regression of LVH by pharmacological means reduces morbidity and mortality over and above reduction in blood pressure.

1.6.1 REGRESSION OF LVH AND PROGNOSIS

A double-blinded, randomized, parallel-group substudy of the LIFE (Losartan Intervention For Endpoint Reduction) study demonstrated that regression of electrocardiographic LVH by Cornell product and/or Sokolow-Lyon voltage criteria during antihypertensive therapy was associated with a lower likelihood of CV morbidity and mortality (129). This was independent of treatment modality and of reductions in BP. In contrast, persistence or development of electrocardiographic LVH by these criteria was associated with increased risk of CV morbidity and mortality. These findings support the value of electrocardiographic LVH criteria for assessing CV risk over time in patients with hypertension and suggest that antihypertensive therapy targeted at regression or prevention of electrocardiographic LVH by these criteria may improve prognosis.

Data from the Heart Outcomes Prevention Evaluation (HOPE) trial provided strong evidence supporting the hypothesis that regression of ECG-LVH improves prognosis (57). The combined end point of either regression of ECG-LVH or prevention of progression to ECG-LVH in response to a Ramipril-based therapy was associated with reduced risk of death, MI, stroke, and congestive heart failure. However, the usefulness of these findings is limited by the low prevalence of ECG-LVH in the HOPE trial (7.1%), the absence of adjustment for other clinical variables in outcome analyses, and by the absence of specific data addressing the value of changes in Sokolow-Lyon voltage for predicting outcome.

A substudy of LIFE by Okin et al (2004) supports the importance of serial measurement of ECG LVH during antihypertensive treatment for risk stratification(129). They found that significantly lower values of both Cornell product and Sokolow-Lyon voltage were associated with 14.5% to 16.6% reductions in the incidence of major CV morbidity and mortality over 4.8 years of follow-up, independent of primary study assignment to Losartan or Atenolol, baseline Framingham risk score, and of baseline and in-treatment levels of BP. Intriguingly, a simultaneous 1-Standard Deviation decrease in both Cornell product and Sokolow-Lyon voltage was associated with a 29% reduction in the composite end point of CV morbidity and mortality (38% decrease risk of CV mortality, 18.9% lower risk of MI and a 26.8% reduced risk of stroke).

The strong, independent relation between lower values of electrocardiographic LVH and reduced rates of CV events in this study is paralleled by findings from the echocardiographic substudies of LIFE, which provide evidence of a similarly powerful association of changing left ventricular mass with CV morbidity and mortality (112, 123, 129, 175, 199). Lower values of left ventricular mass were associated with a 22% lower rate of composite end points, a 38% reduction in CV mortality, a 24% reduction in stroke, and a 15% lower rate of MI. Lack of regression of LVH in these studies also portends a poorer prognosis.

Taken together, these electrocardiographic and echocardiographic findings demonstrate that the strong association between serial assessments of LVH and CV outcomes is independent of the method used to serially assess the degree of hypertrophy. What is clear is that regression of LVH improves patients prognosis drastically and either development of LVH or lack of regression is an omen for a dismal prognosis.

1.7 LVH REGRESSION AND PHARMACOLOGY

For many years, clinicians have been interested in finding the best drugs to regress LVH or improve other surrogate markers of hypertensive target organ damage (such as microproteinuria or endothelial dysfunction). One meta-analysis which included only double-blind, randomized, controlled clinical studies with parallel-group design (39 trials) found that more LVH regression occurred with greater blood pressure reduction and a longer duration of therapy (205). Specifically, LVH regression occurred in 13% of patients treated with the ACE inhibitors, 9% treated with calcium channel blockers, 6% treated with ß-blockers, and 7% treated with diuretics, suggesting that overall, the ACE inhibitors (or ARBs) are probably the best drugs for LVH regression.

The LVH regression substudy from the Heart Outcomes Prevention Evaluation (HOPE) trial, which studied a broad range of patients with normal or controlled blood pressure, showed that ECG-LVH was regressed in 46.1% of patients treated with Ramipril compared with 38.6% of those treated with placebo (198). Importantly, this effect was independent of hypertension or blood pressure reduction. Furthermore, LVH prevention/regression using Ramipril resulted in a reduction of the primary outcomes (cardiovascular death, myocardial infarction, or stroke) and the prevention of congestive heart failure. This study represents one of the first trials that convincingly shows

that LVH regression really does matter, even in patients without hypertension. Unfortunately, the study depends on ECG criteria of LVH, and it is recognized that although the ECG is a useful screening tool for LVH, it has a relatively low specificity and sensitivity compared to echocardiography.

The use of ACE inhibitors is well-established for the treatment of hypertension, heart failure, left ventricular systolic dysfunction, and perhaps for all patients with myocardial infarction, diabetic nephropathy and diabetic retinopathy. Data from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) also point toward the beneficial effects of the ACE inhibitor, Perindopril, in patients after stroke. Therefore, it is possible that ACE inhibitors may be the best drugs for regressing LVH and result in corresponding improvements in prognosis through their benefits in concomitant comorbidity, including underlying left ventricular dysfunction, diabetes, renal dysfunction, cerebrovascular disease.

The pathophysiology of cardiovascular disease and in particular LVH may help us understand why ACE inhibitors provide therapeutic hope to the many patients with cardiovascular disease and LVH. The most obvious system influenced by ACE inhibitors is the renin-angiotensin-aldosterone system. Because angiotensin and aldosterone have deleterious effects on myocardial and vascular remodeling, the beneficial effects of these drugs may come through the blockade of these neurohormones, resulting in an antihypertrophic effect on the myocardium and an antiproliferative effect on smooth muscles.

Furthermore, despite blood vessels being exposed to higher pressures, the complications of hypertension (that is, myocardial infarction and stroke) are paradoxically thrombotic rather than hemorrhagic. As mentioned previously, abnormalities of haemostasis, platelets, and endothelial dysfunction are present in hypertension and LVH, contributing to a prothrombotic state.

Hypertension and other vascular diseases are associated with endothelial dysfunction. ACE inhibitors have been shown to improve endothelial function. There is also some evidence that the ACE inhibitors may also improve insulin resistance. Nevertheless, unanswered questions remain. For example, the Afro-Caribbean ethnic groups are at particular risk of developing LVH, and it remains uncertain whether LVH regression in this group would translate into a prognostic benefit. Ethnic differences in cardiovascular disease are increasingly important considerations, and in the United Kingdom, blacks are at high risk of hypertension and hypertension-related complications such as stroke and renal damage, whereas south Asians are at a high risk of coronary artery disease. Indeed, the recent analysis from the Studies of Left Ventricular Dysfunction (SOLVD) investigators suggests that black patients with left ventricular dysfunction do not respond well to ACE inhibitors, especially if they have a past history of hypertension. Limited data on LVH regression and other hypertensive target organ damage are available in south Asians, although it is perceived that they respond to antihypertensive drugs similarly to whites.

In this study I set out to assess how prevalent LVH is in PAD patients and to elucidate its relation to blood pressure. If it is indeed prevalent then its burden on morbidity and mortality may potentially be significant in this group of patients. Targeting the RAAS may be a powerful tool to improve the outcome for these patients.

CHAPTER 2

MATERIALS AND METHODS

2.1 Study Population and Sample Size Estimates

I gained Ethical Approval from the Tayside Committee on Medical Research Ethics and the study was undertaken in accordance with their standards. Three hundred and fifty patients who were referred as outpatients for the first time because of PAD were consecutively recruited at Ninewells Hospital, Dundee, between March 2003 and June 2004. Six hundred and thirty one patients were approached by letter until 350 agreed to participate in the study. Sample size estimates were performed by Dr Simon Ogston (Senior Lecturer in Statistics, Department of Epidemiology, Ninewells Hospital). Sample size calculations are based on expecting the prevalence of LVH in PAD patients to be 30%. This figure is based on the prevalence of LVH in analogous populations to be approximately 35%. Studies from this institution (University of Dundee) demonstrated that 52% of angina patients, 42% of type 2 diabetics, 25% in a random group of stroke survivors and 25% in a random group of patients attending a geriatric day hospital have evidence of LVH (13, 14, 206). This means that a sample size of 323 PAD patients would be required to give a precision (standard error) of 2.5% in assessing the expected prevalence i.e. this would give a two sided confidence interval of 95%. The standard error of a prevalence estimate in a population is:

$$\sqrt{(P(1-P)/n)}$$

where n=total number of subjects being studied, P= expected prevalence of an abnormality expressed as a decimal (e.g. if the prevalence is 30% then P=0.3).

i.e. if we expect the prevalence of LVH to be 30% and we study 323, then the standard error will be:

$$\sqrt{(0.3(1-0.3)/323)} = \sqrt{0.00065} = 0.025$$

Expressed as a percentage, this gives a standard error of 2.5%.

The inclusion criteria were a history of intermittent claudication and the presence of a low (≤0.9) ankle brachial pressure index. The exclusion criteria included:

(1) Patients with valvular, pericardial or congenital heart disease

(2) Patients with an impaired left ventricular systolic function on echocardiography (EF<45%).

(3) Patients with ABPI <0.5

Subjects were approached by letter from a database detailing new referrals to the Vascular Laboratory in Ninewells Hospital, Dundee (Sample letter in Appendix). All subjects who volunteered for the study attended a single clinic visit in the hospital and underwent the following: routine history, clinical examination, electrocardiography, routine blood tests, transthoracic echocardiography and 24 hour ambulatory Blood Pressure monitoring. (Consent form and reporting form in Appendix). Hypertension on office BP

was taken as a BP of >140/90 mmHg as in the Joint British Societies (JB2) guidelines (2005).

2.2 ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed by a single operator (Dr Gary Wright) using a Hewlett Packard Sonos 5500 (Andover, MA, USA) Echocardiographic machine. The scan was performed with the patient lying in the left lateral position at approximately 45°.

2.2.1 Left ventricular hypertrophy assessment

Patients were studied with two-dimensional guided M-mode echocardiography in standard views. All measurements were made according to the American Society of Echocardiography (ASE) recommendation at end diastole, taken as the onset of QRS complex. The leading edge to leading edge convention was used to measure interventricular septal (IVS) thickness, left ventricular internal diameter (LVIDD) and left ventricular posterior wall thickness (PWT). Measurements were made over at least 3 separate cardiac cycles and the average taken. Left ventricular mass (LVM) was calculated according to the formula of Devereux et al.

0.80 (ASE left ventricular mass) +0.6 (83)

and indexed to body surface area (BSA) to give a left ventricular mass index (LVMI). Left ventricular hypertrophy was defined as LVMI greater than **110g/m^2 in females** and greater than **134 g/m^2 in males**. Left ventricular mass was also indexed to height $^{2.7}$ and LVH was defined as LVMI greater than **47g/m$^{2.7}$ in females** and greater than **50g/m$^{2.7}$ in males**. LVMI was not calculated in cases in which either poor image quality or inadequate image alignment prevented accurate M-mode measurements from being made.

Left ventricular geometry was classified as normal, concentric remodeling, eccentric left ventricular hypertrophy or concentric left ventricular hypertrophy, based on left ventricular mass and relative wall thickness (RWT). RWT was calculated as follows:

2 x LV posterior wall thickness/ LV end diastolic dimension X 100%.

A value of > 45% was defined as abnormal.

- Normal LV geometry was defined as normal left ventricular mass and normal RWT
- Concentric remodeling defined as normal left ventricular mass and increased RWT
- Eccentric LVH defined as increased left ventricular mass and normal RWT

- Concentric LVH defined as increased left ventricular mass and increased RWT.

2.2.2 Left ventricular systolic function assessment

Quantitative assessment of left ventricular systolic function was made using the modified biplane Simpson's method to calculate a left ventricular ejection fraction. Three measurements from successive cardiac cycles were made in the two chamber and four chamber views.

2.3 BLOOD PRESSURE ASSESSMENT

2.3.1 Office Blood Pressure

Blood pressure was taken in the seated position, on the non-dominant arm (brachial artery) using a calibrated OMRON sphygmomanometer (Omron Healthcare Europe, Hoofddorp, Netherlands) after a period of 15 minutes rest using an appropriate size cuff. The average of 3 consecutive measurements was used.

2.3.2 Ambulatory Blood Pressure (24 Hour)

Ambulatory BP monitoring was performed with Meditech ABPM-04 (Meditech Ltt, Budapest, Hungary) recorders on a day of typical activity in 131 patients fitted to the non-dominant arm. Those who underwent the test

were randomly chosen due to the availability of the machines, with a bias toward those patients with echocardiographic LVH. Ambulatory BP readings were obtained at 15 min intervals from 8 am to 10 pm (daytime period) and 30 min intervals from 10 pm to 8 am (night time period). The following ambulatory BP parameters were evaluated: average daytime, average night time and 24 hour systolic and diastolic BP. Subjects included in the study analysis had recordings of good technical quality (at least 70% of valid readings).

2.4 BLOOD SAMPLES

Blood samples were taken from an antecubital vein and sent for analysis to Ninewells Hospital Biochemistry laboratory for total cholesterol, HDL cholesterol, serum creatinine (5ml of clotted blood). Four milliliters of whole blood EDTA samples were taken for near patient BNP testing using the Biosite® Triage BNP fluorescence immunoassay test kit (Biosite® Inc, San Diego, CA, USA).

Normal ranges for blood tests:

Test	Male Range	Female Range
Creatinine	62-106μmol/L	44-80μmol/L
Total Cholesterol	<5.0 mmol/L	<5.0mmol/L
HDL Cholesterol	>1.0 mmol/L	>1.2 mmol/L
BNP	<100 pg/ml	<100pg/ml

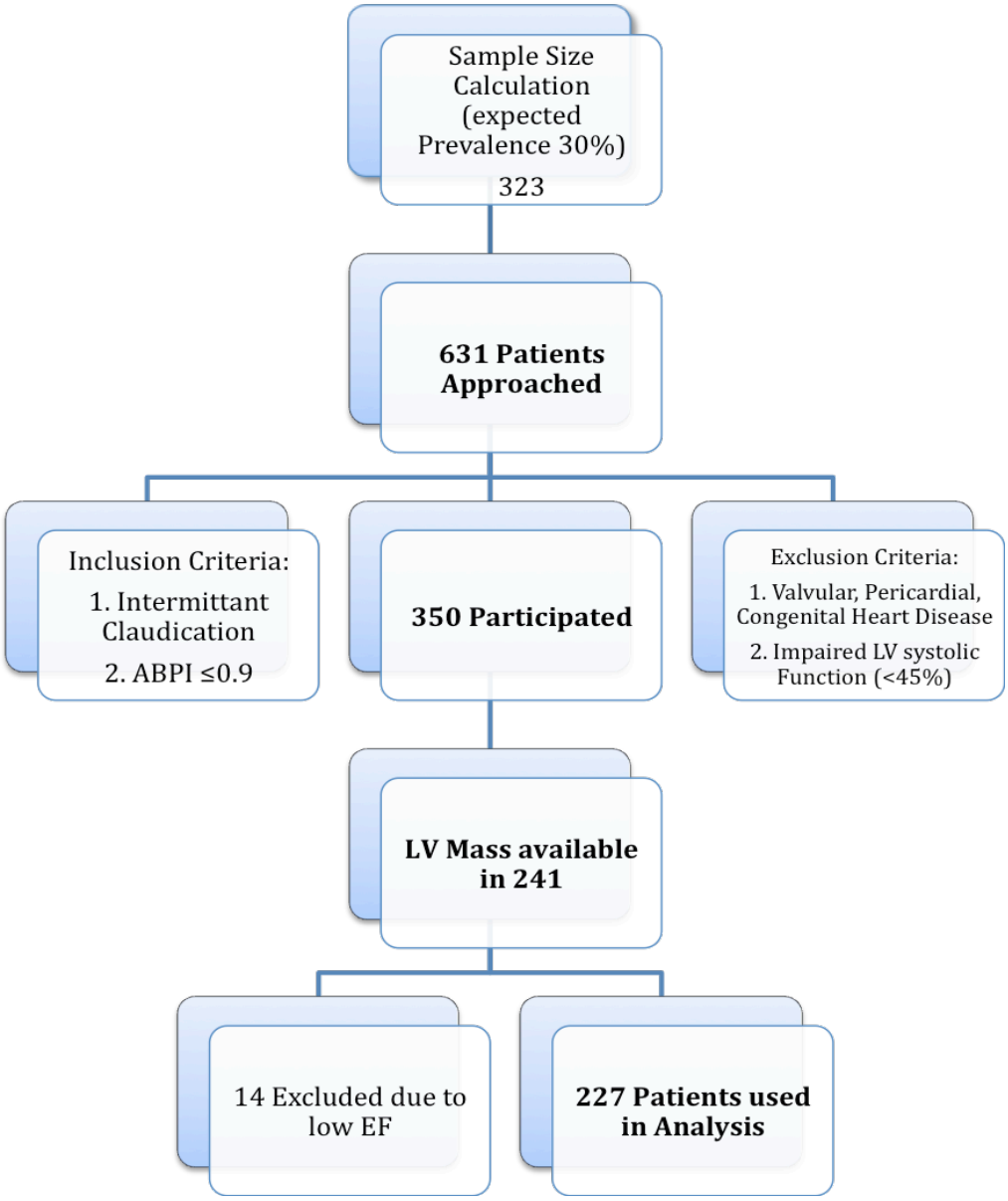
2.5 STATISTICS

Values are quoted as means and 95% confidence intervals. A minimum of three measurements were used to calculate the mean for each parameter. Comparisons of continuous variables, such as blood pressure, between groups were performed using the one-way ANOVA test. The one-way ANOVA test is useful when the variables are not in a normal distribution and can tolerate data that is not in a typical bell shaped curve. Comparisons between categorical variables, such as presence or absence of LVH, were performed using the chi-square test. Multivariate forward regression analysis was performed to establish which variables were independently related to left ventricular mass. All statistical analyses were performed using SPSS for Windows version 13.0. A value of $p<0.05$ was considered to be statistically significant. See section **2.1 Study Population** for a more in-depth explanation of sample size calculations and rationale. Sample size calculations were performed by Dr Simon Ogston (Senior Lecturer in Statistics, Department of Epidemiology, Ninewells Hospital). Sample size calculations are based on expecting the prevalence of LVH in PAD patients to be 30%. This figure is based on the prevalence of LVH in analogous populations to be approximately 35% as stated above.

CHAPTER 3

RESULTS

The following consort diagram shows a flowchart of recruitment with six hundred and thirty one patients being approached resulting in three hundred and fifty participants in the study. Analysis was carried out in two hundred and twenty seven patients as LV mass was available in two hundred and forty one. Fourteen patients were excluded because of an LV ejection fraction of less that forty five percent.


Sample Size Calculation (expected Prevalence 30%)
323
631 Patients Approached
Inclusion Criteria:
1. Intermittant Claudication
2. ABPI ≤0.9
350 Participated
Exclusion Criteria:
1. Valvular, Pericardial, Congenital Heart Disease
2. Impaired LV systolic Function (<45%)
LV Mass available in 241
14 Excluded due to low EF
227 Patients used in Analysis

3.1 ECHOCARDIOGRAPHIC LEFT VENTRICULAR HYPERTROPHY (INDEXED TO BODY SURFACE AREA)

Patient characteristics of the 350 patients recruited are listed in **Table 3.1**. M-mode measurement of LV mass was obtainable in 241 patients (69%). Those in whom M-mode LV mass could not be assessed did not differ significantly in any other parameters from those in whom an adequate M-mode measurement was obtained (**Table 3.2**). Out of the 241 patients with M-mode LV mass, 14 patients were excluded due to low ejection fraction. Of the remaining 227 patients with preserved LV systolic function, the proportion of patients with LVH was 50% (114/227) when left ventricular mass was indexed to body surface area (BSA). **Table 3.3** shows the characteristics of patients with and without left ventricular hypertrophy. The data was normally distributed, with similar mean, median and modes, with a typical bell shaped curve for all the continuous variables. Multiple regression analysis was performed to include all possible determinants of left ventricular mass index: age, sex, body mass index (BMI), history of hypertension, previous myocardial infarction (MI), diabetes mellitus, ischaemic heart disease, systolic blood pressure, creatinine and total cholesterol. This model explained only 11.4% of the variation in LVMI, and the factors independently related to LVMI were **age** (standardised β= 0.208, p=0.002), **sex** (standardised β= 0.215, p=0.001) and **diabetes** (standardised β= 0.169, p=0.009). Notably systolic BP was not an independent predictor. Patients with LVH were significantly more likely to be prescribed a beta-blocker (27% vs. 12%, p=

0.007), ACE inhibitor (48% vs. 24%, p<0.001) and nitrate (18% vs. 5%, p=0.006). 35% of the studied patients (79/227) had a normal LV geometry calculated according to body surface area (**Figure 3.1**).

The association between history of hypertension, clinic BP and the presence/ absence of LVH is shown in **Figure 3.2**. 64% of the study population had a history of hypertension (n=145). In this group of patients, 13% were normotensive and had LVH. In the group of patients without a history of hypertension (n=82), 17% were normotensive and had evidence of LVH. Overall, 14% of the entire study population had echo LVH despite a normal clinic BP (**Figure 3.3**). The equivalent data using a lower office BP cutoff (<130/80) are shown for completeness (**Figure 3.4**).

3.2 ECHOCARDIOGRAPHIC LEFT VENTRICULAR HYPERTROPHY (INDEXED TO HEIGHT$^{2.7}$)

The proportion of patients with LVH was 72% (163/227) when left ventricular mass was indexed to height$^{2.7}$. **Table 3.4** shows the characteristics of patients with and without left ventricular hypertrophy. Multiple regression analysis was performed to include all possible determinants of left ventricular mass index: age, sex, body mass index (BMI), history of hypertension, previous myocardial infarction (MI), diabetes mellitus, ischaemic heart disease, systolic blood pressure, creatinine and total cholesterol. This model explained only 15.2% of the variation in LVMI, and the factors independently related to LVMI were **age** (standardised β=0.227, p=<0.001), **BMI** (standardised β= 0.274, p<0.001) and **diabetes** (standardised β= 0.141, p=0.029). Again systolic BP was not an independent predictor. Patients with LVH were significantly more likely to be prescribed a beta-blocker (24% vs. 8%, p= 0.005), ACE inhibitor (41% vs. 22%, p=0.008), statin (76% vs. 61%, p=0.032), diuretic (44% vs. 28%, p=0.035) and nitrate (16% vs. 0%, p=0.001). Concentric LVH was the most common geometry pattern (38%, 86/227) with 23% (52/227) of patients having normal geometry (**Figure 3.5**).

The association between history of hypertension, clinic BP and the presence/ absence of LVH is shown in **Figure 3.6**. In the group of patients without a history of hypertension (n=82), 33% were normotensive and had evidence of LVH. Overall, 24% of the entire study population (n=227) had echo LVH

despite a normal clinic BP (**Figure 3.7**). The equivalent data using a lower office BP cutoff (<130/80) are shown for completeness (**Figures 3.8**). Even using this lower cutoff, 16% of LVH patients had a normal BP, irrespective of which LV mass criteria are applied.

3.3 AMBULATORY BLOOD PRESSURE (24 HOUR)

3.3.1 LVH indexed to Body Surface Area

24 hour ambulatory blood pressure readings were carried out in 64% of the LVH patients (73/114) and 51% of the non-LVH patients (58/113). Those who underwent this test were randomly chosen purely due to the availability of spare 24 hour Blood pressure monitoring equipment, albeit with a bias towards performing this test more frequently in patients with LVH than those without LVH because the LVH patients were obviously of more interest here.

Mean ambulatory systolic blood pressure was significantly lower in the non-LVH group compared to the LVH group (**Table 3.5**). There was no significant difference in the mean diastolic blood pressure reading in both groups. The percentage of patients with a normal ambulatory BP reading was not significantly different in both the LVH and non-LVH group. 40% of the patients in the LVH group had a normal 24-hour ABPM reading.

The data for the number of patients in each group in **Figure 3.9** were adjusted to represent the whole PAD population rather than just the subset who received ABPM, taking into account the bias toward measuring ABPM in those with LVH. Approximately every 1 in 2 patients in this study had a normal ABPM reading. In this normotensive group, 43% of the patients had LVH. In fact, a rough summary of the data in **Figure 3.9** is that half of the patients had LVH and a somewhat different half had a high BP. PAD patients

fall into four equal groups: one quarter had LVH and a high BP, another two quarters had either LVH or a high BP and another quarter had neither LVH nor a high BP.

3.3.2 LVH indexed to Height $^{2.7}$

Mean ambulatory systolic blood pressure was significantly lower in the non-LVH group compared to the LVH group (**Table 3.6**). There was no significant difference in the mean diastolic blood pressure reading in both groups. The percentage of patients with a normal 24-hour BP reading was not significantly different in both the LVH and non-LVH group. 41% of the patients in the LVH group had a normal 24-hour ABPM reading. The data for the number of patients in each group in **Figure 3.10** were adjusted to represent the whole PAD population rather than just the subset who received ABPM, taking into account the bias toward measuring ABPM in those with LVH. Approximately every 1 in 2 patients in this study had a normal ABPM reading. In this normotensive group, 63% of the patients had LVH.

3.4 SEVERITY OF PERIPHERAL ARTERIAL DISEASE, HISTORY OF ATRIAL FIBRILLATION AND MYOCARDIAL INFARCTION IN PATIENTS WITH AND WITHOUT LEFT VENTRICULAR HYPERTROPHY

There was no difference in the severity of PAD, in terms of ABPI, in patients with or without LVH (**Table 3.3 and 3.4**). There was a mean ABPI of 0.68 in patients with LVH according to BSA compared to 0.69 in patients without LVH. The ABPI was the same (0.69) in patients with and without LVH according to height $^{2.7}$.

Out of two hundred and twenty seven patients studied, there were fourteen (6%) who had atrial fibrillation (AF) on a 12-lead ECG performed during the assessment (**Table 3.7**). The patients with AF had a higher mean LVMI of **189.2g/m^2** compared to **130.7g/m^2** in those in sinus rhythm at the time of assessment (*p<0.001*). Despite a higher mean mass, there was no statistical difference in percentage of patients with LVH between those patients with or without AF (64% V 49%, *p=0.279*). Unsurprisingly, patients with AF had a larger left atrial diameter (4.08cm V 3.34cm, *p<0.001*), smaller LV ejection fraction (58% V 67%, *p=0.009*) and had a significantly higher BNP (195pg/ml V 75pg/ml, *p<0.001*). Patients who were in AF were less likely to have a smoking history (64% V 90%, *p=0.003*) compared to those in sinus

rhythm. All other parameters were similar and in particular, there was no difference in either clinic blood pressure or history of hypertension between those in AF or sinus rhythm.

Patients with a history of myocardial infarction were more likely to have LVH than those without (69% V 47%, *p=0.024*), although their mean LV mass was statistically similar (**150.5g/m^2** V **131.6g/m^2**, *p=0.059*) compared to patients with no history of prior MI (**Table 3.8**). Patients with a history of MI were more likely to be male (81% V 59%, *p=0.015*) and have a lower total cholesterol (4.16mmol/L V 4.60mmol/L, *P=0.004*). This is likely to be because more patients with a prior MI were prescribed a Statin (91% V 69%, *P=0.01*). There was no difference in office systolic blood pressure, but patients with prior MI had a lower diastolic blood pressure (72mmHg V 78mmHg, *p=0.002*). This is likely to be because patients with a prior MI are more likely to be prescribed anti-hypertensive agents such as beta blockers (38% V 17%, P<0.001), ACE inhibitors (52% V 33%, *p=0.046*) and calcium channel receptor antagonists (53% V 35%, *p=0.048*). Importantly, there was no difference in ejection fraction (65% V 67%, *p=0.493*) between those with and without a history of MI.

Table 3.1: Patient characteristics (mean +/-SD) of the 350 subjects studied

Variable	Mean (SD)
Males (%)	65.1
Age (years)	68.9 (9.5)
BMI (kg/m2)	28.3 (4.6)
Office systolic BP (mmHg)	147 (21)
Office diastolic (mmHg)	77 (11)
Creatinine (μmol/L)	107 (50)
Total Cholesterol (mmol/L)	4.57 (0.95)
HDL Cholesterol (mmol/L)	1.42 (0.46)
History of hypertension (%)	61.4
History of Type II Diabetes (%)	18.3
Current smokers (%)	39.1
Ex-smokers (%)	50.5
History of ischaemic heart disease (%)	32.9
Previous MI (%)	16.9
LVMI	
Males	146.5 (61.7)
Females	123 (38.7)
Left Ventricular Ejection Fraction (%)	64.6 (12.1)

Treated with	
Aspirin	70
Statin	71.7
Beta blockers	18
ACE inhibitors	36.8
Angiotensin receptor blocker (ARB)	9.7
Clopidogrel	8
Calcium Antagonist	38.6
Nicorandil	4
Nitrate	13.4
Diuretic	40.9

BMI – Body Mass Index
BP – Blood Pressure
MI – Myocardial Infarction
LVMI – Left Ventricular Mass Index
ACE – Angiotensin Converting Enzyme

Table 3.2: Patient characteristics classified according to presence or absence of M-mode LV mass measurements being obtainable.

Variable	**LVM available** mean (SD) (n=241)	**No LVM available** mean (SD) (n=109)	**P value**
Males (%)	63	71	0.183
Age (years)	68 (10)	70 (9)	0.089
BMI (kg/m^2)	28.2 (4.4)	28.4 (4.8)	0.698
Clinic systolic BP (mmHg)	147 (21)	147 (23)	0.939
Clinic diastolic BP (mmHg)	77 (11)	77 (11)	0.872
Creatinine (μmol/L)	107 (57)	108 (31)	0.811
Total Cholesterol (mmol/L)	4.52 (0.96)	4.67 (0.94)	0.157
Ex/current smoker (%)	89	92	0.453
History of hypertension (%)	63	58	0.407
D.M. (%)	19	17	0.882
History of MI (%)	16	18	0.645

BMI – Body Mass Index
D.M. – Diabetes Mellitus
MI – Myocardial Infarction

Table 3.3: Patient characteristics classified according to presence or absence of left ventricular hypertrophy indexed to body surface area.

Variable	LVH mean (n=114)	No LVH mean (n=113)	P value
Males %	60	65	0.495
Age (years)	71	65	**<0.001**
BMI (kg/m2)	29.0	27.6	**0.014**
ABPI	0.68	0.69	0.806
Clinic systolic BP (mmHg)	151	143	**0.002**
Clinic diastolic BP (mmHg)	76	78	0.123
History of hypertension (%)	70	58	0.054
History of type II Diabetes (%)	28	11	**0.001**
Previous MI (%)	19	9	**0.035**
IHD (%)	42	22	**0.002**
Current smokers (%)	31	44	**0.040**
BNP (pg/ml)	105	57	**0.001**
Creatinine (μmol/L)	107	97	**0.010**
Total Cholesterol (mmol/l)	4.47	4.59	0.325
HDL Cholesterol (moml/l)	1.39	1.44	0.342
LVMI (g/m2)			
Males	184.3	102.4	**<0.001**
Females	148.5	91	**<0.001**
LV ejection fraction (%)	66	68	0.216

IVS (cm)	1.35	1.00	**<0.001**
LVID (cm)	5.10	4.67	**<0.001**
PWT (cm)	1.21	0.93	**<0.001**
Left atrial diameter (cm)	3.55	3.26	**0.036**

BMI – Body Mass Index
MI – Myocardial Infarction
IHD – Ischaemic Heart Disease
BNP - B-Type Natriuretic Peptide
LVMI - Left Ventricular Mass Index
LV – Left Ventricle
IVS – Interventricular Septum
LVID – Left Ventricular Internal Dimension
PWT – Posterior Wall Thickness

Table 3.4: Patient characteristics classified according to presence or absence of left ventricular hypertrophy indexed to height 2.7.

Variable	LVH mean (n=163)	No LVH mean (n=64)	P value
Males % (n)	62	63	1.00
Age (years)	70	64	**<0.001**
BMI (kg/m2)	29.0	26.7	**<0.001**
ABPI	0.69	0.69	0.947
Clinic systolic BP (mmHg)	149	143	0.064
Clinic diastolic BP (mmHg)	76	79	0.051
History of hypertension (%)	67	56	0.167
History of type II Diabetes (%)	25	6	**0.002**
Previous MI (%)	18	5	**0.010**
IHD (%)	40	13	**<0.001**
Current smokers (%)	34	47	0.070
BNP (pg/ml)	93	54	**0.016**
Creatinine (umol/L)	112	94	**0.042**
Total Cholesterol (mmol/l)	4.54	4.52	0.911
HDL Cholesterol (moml/l)	1.40	1.46	0.425
LVMI (height 2.7)			
Males	77.2	41.4	**<0.001**
Females	70.3	42	**<0.001**
LV ejection fraction (%)	66	68	0.403

IVS (cm)	1.27	0.93	**<0.001**
LVID (cm)	4.98	4.62	**<0.001**
PWT (cm)	1.15	0.88	**<0.001**
Left atrial diameter (cm)	3.49	3.10	**0.021**

BMI – Body Mass Index
MI – Myocardial Infarction
IHD – Ischaemic Heart Disease
BNP - B-Type Natriuretic Peptide
LVMI - Left Ventricular Mass Index
LV – Left Ventricle
IVS – Interventricular Septum
LVID – Left Ventricular Internal Dimension
PWT – Posterior Wall Thickness

Table 3.5: 24 hour ambulatory blood pressure results classified according to presence or absence of LVH (indexed to body surface area)

Variable	LVH mean (n=73)	No LVH mean (n=58)	P value
24 hour systolic (mmHg)	137	130	**0.005**
24 hour diastolic (mmHg)	67	70	0.078
DT systolic (mmHg)	141	135	**0.015**
DT diastolic (mmHg)	71	74	**0.027**
NT systolic (mmHg)	131	123	**0.005**
NT diastolic (mmHg)	63	64	0.346
Normal 24 hour BP (≤130/80) (%)	40	52	0.216
Normal DT reading (≤135/85) (%)	40	50	0.289
Normal NT reading (≤120/70) (%)	25	42	0.058
Abnormal 24 hour BP (>135/85) (%)	52	38	0.116
Abnormal DT reading (>140/90) (%)	51	31	**0.032**
Abnormal NT reading (>125/75) (%)	66	49	0.071

DT – Day Time
NT – Night Time

Table 3.6: 24 hour ambulatory blood pressure results classified according to presence or absence of LVH (indexed to height 2.7)

Variable	LVH mean (n=101)	No LVH mean (n=30)	P value
24 hour systolic (mmHg)	136	128	**0.009**
24 hour diastolic (mmHg)	68	71	0.116
DT systolic (mmHg)	140	133	**0.034**
DT diastolic (mmHg)	71	76	**0.012**
NT systolic (mmHg)	130	120	**0.007**
NT diastolic (mmHg)	63	64	0.704
Normal 24 hour BP (≤130/80) (%)	41	60	0.094
Normal DT reading (≤135/85) (%)	40	60	0.060
Normal NT reading (≤120/70) (%)	28	50	**0.027**
Abnormal 24 hour BP (>135/85) (%)	47	30	0.142
Abnormal DT reading (>140/90) (%)	45	30	0.206
Abnormal NT reading (>125/75) (%)	57	40	0.143

DT – Day Time
NT – Night Time

Table 3.7: Patient characteristics classified according to presence or absence of Atrial Fibrillation (AF) on 12 lead ECG

Variable	AF mean (n=14)	No AF mean (n=213)	P value
Males %	64	62	0.083
Age (years)	77	68	**<0.001**
BMI (kg/m2)	28.2	28.3	0.934
ABPI	0.62	0.69	0.123
Clinic systolic BP (mmHg)	149	147	0.705
Clinic diastolic BP (mmHg)	80	77	0.221
History of hypertension (%)	71	63	0.546
History of type II Diabetes (%)	14	20	0.620
Previous MI (%)	21	14	0.418
IHD (%)	43	31	0.379
Smokers (current or ex) (%)	64	90	**0.003**
BNP (pg/ml)	195	75	**<0.001**
Creatinine (μmol/L)	105.6	107.0	0.932
Total Cholesterol (mmol/l)	4.54	4.26	0.301
HDL Cholesterol (mmol/l)	1.42	1.44	0.827
LVMI (g/m^2)	189.2	130.7	**<0.001**
LV ejection fraction (%)	58	67	**0.009**
LVH (%)	64	49	0.279
LVID (cm)	5.30	4.85	**0.02**

PWT (cm)	1.08	1.07	0.888
Left atrial diameter (cm)	4.08	3.34	**<0.001**

Table 3.8: Patient characteristics classified according to History of prior Myocardial Infarction (MI)

Variable	MI mean (n=32)	No MI mean (n=195)	P value
Males %	81	59	**0.015**
Age (years)	68	68	0.842
BMI (kg/m2)	29.7	28.1	0.063
ABPI	0.72	0.68	0.301
Clinic systolic BP (mmHg)	142	148	0.102
Clinic diastolic BP (mmHg)	72	78	**0.002**
History of hypertension (%)	66	64	0.825
History of type II Diabetes (%)	28	18	0.179
Angina (%)	94	22	**0.001**
Smokers (current or ex) (%)	88	89	0.842
BNP (pg/ml)	85	81	0.856
Creatinine (μmol/L)	109	107	0.849
Total Cholesterol (mmol/l)	4.16	4.60	**0.004**
HDL Cholesterol (moml/l)	1.32	1.43	0.182
LVMI (g/m^2)	150.5	131.6	0.059
LV ejection fraction (%)	65	67	0.493
LVH (%)	69	47	**0.024**
LVID (cm)	5.29	4.81	**<0.001**
PWT (cm)	1.09	1.07	0.740

Left atrial diameter (cm)	3.67	3.38	0.154

Figure 3.1: Left ventricular geometry in the studied population, using left ventricular mass indexed to body surface area

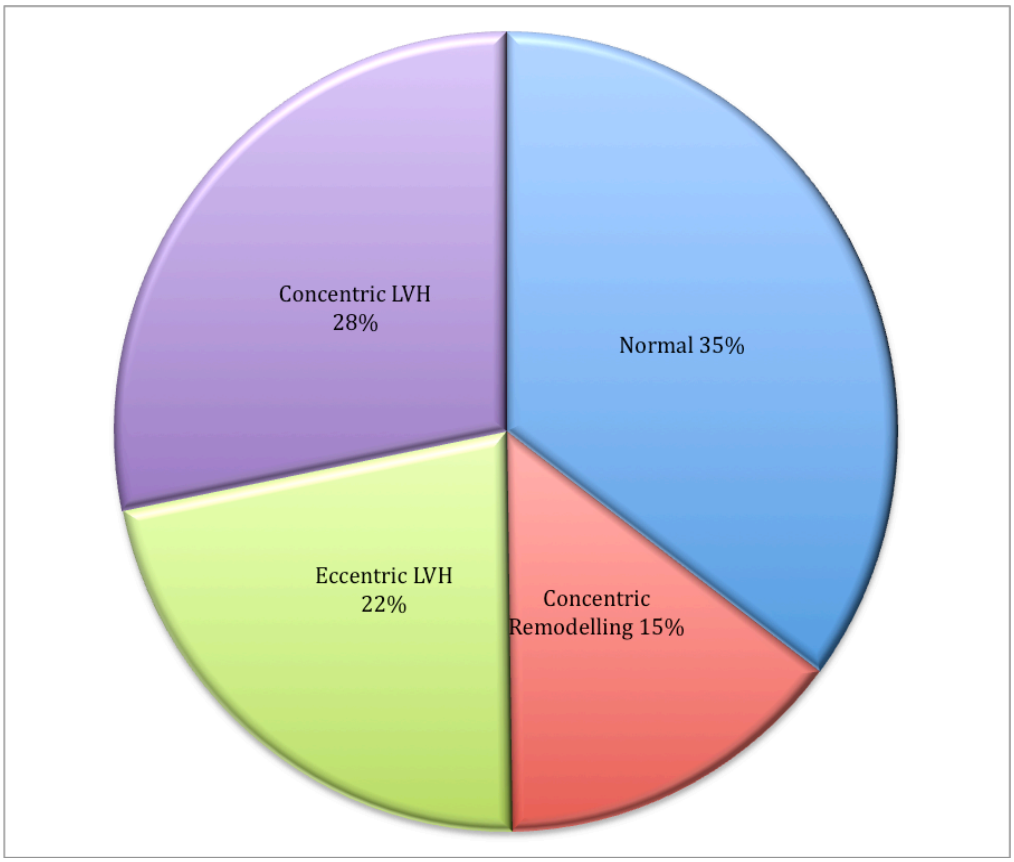
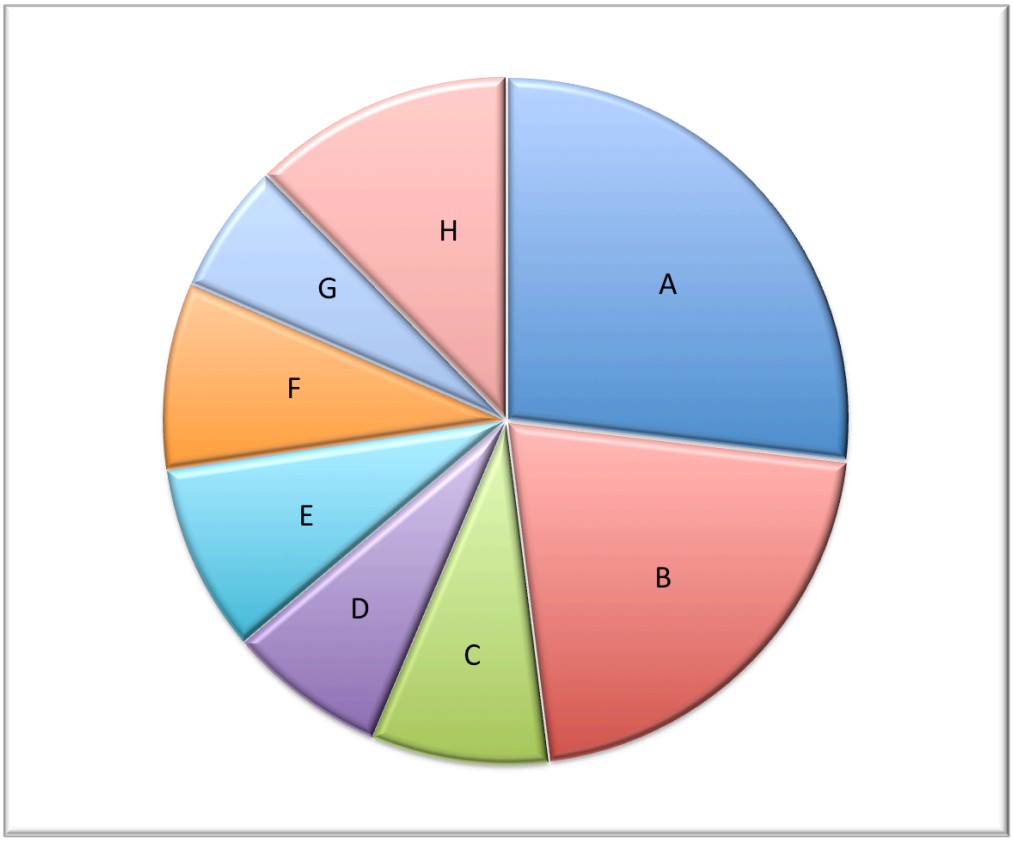


Figure 3.2: Association between history of hypertension, clinic BP (normal clinic BP <140/90) and presence or absence of LVH (indexed to BSA) in this study population



A History of Hypertension, High Clinic BP, LVH 28%

B History of Hypertension, High Clinic BP, No LVH 21%

C History of Hypertension, Normal Clinic BP, LVH 8%

D History of Hypertension, Normal Clinic BP, No LVH 7%

E No History of Hypertension, High Clinic BP, LVH 9%

F No History of Hypertension, High Clinic BP, No LVH 9%

G No History of Hypertension, Normal Clinic BP, LVH 6%

H No History of Hypertension, Normal Clinic BP, No LVH 12%

Figure 3.3 Association with Clinic Blood Pressure and presence or absence of LVH (indexed to BSA) in the study population.

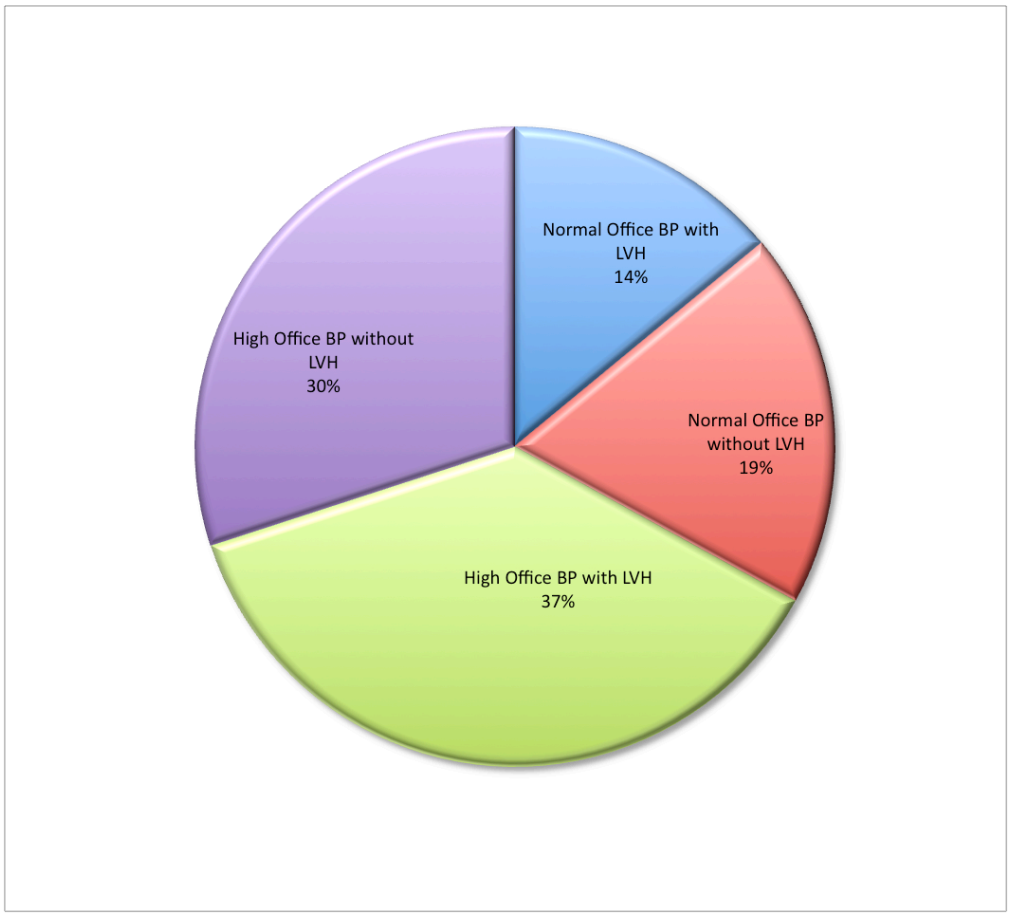
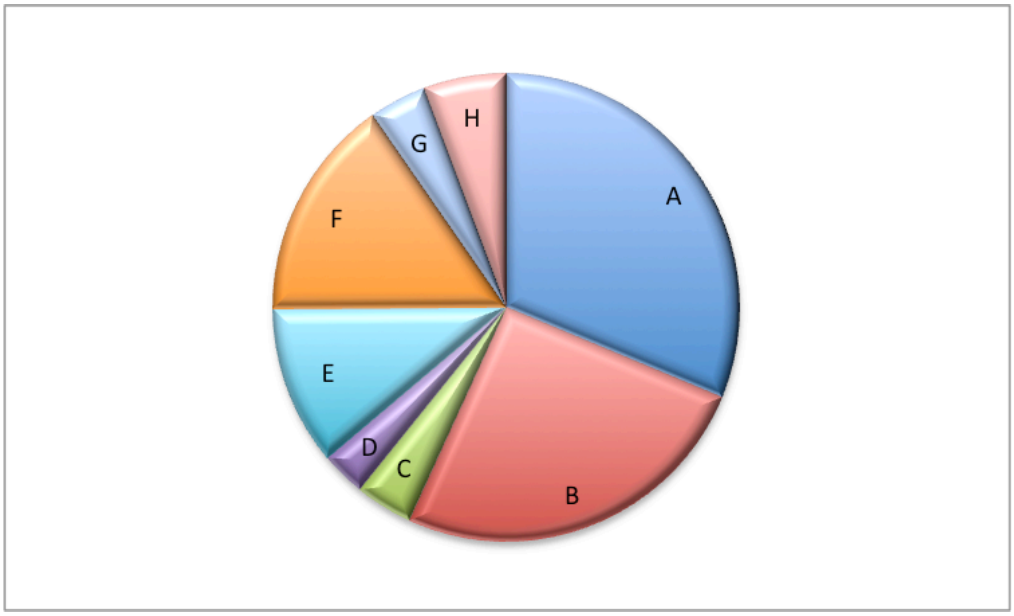


Figure 3.4: Association between history of hypertension, clinic BP (normal clinic BP <130/80) and presence or absence of LVH (indexed to BSA) in this study population



A History of Hypertension, High Clinic BP, LVH 31%

B History of Hypertension, High Clinic BP, No LVH 26%

C History of Hypertension, Normal Clinic BP, LVH 4%

D History of Hypertension, Normal Clinic BP, No LVH 3%

E No History of Hypertension, High Clinic BP, LVH 11%

F No History of Hypertension, High Clinic BP, No LVH 15%

G No History of Hypertension, Normal Clinic BP, LVH 4%

H No History of Hypertension, Normal Clinic BP, No LVH 6%

Figure 3.5: Left ventricular geometry in the studied population, using left ventricular mass indexed to height $^{2.7}$

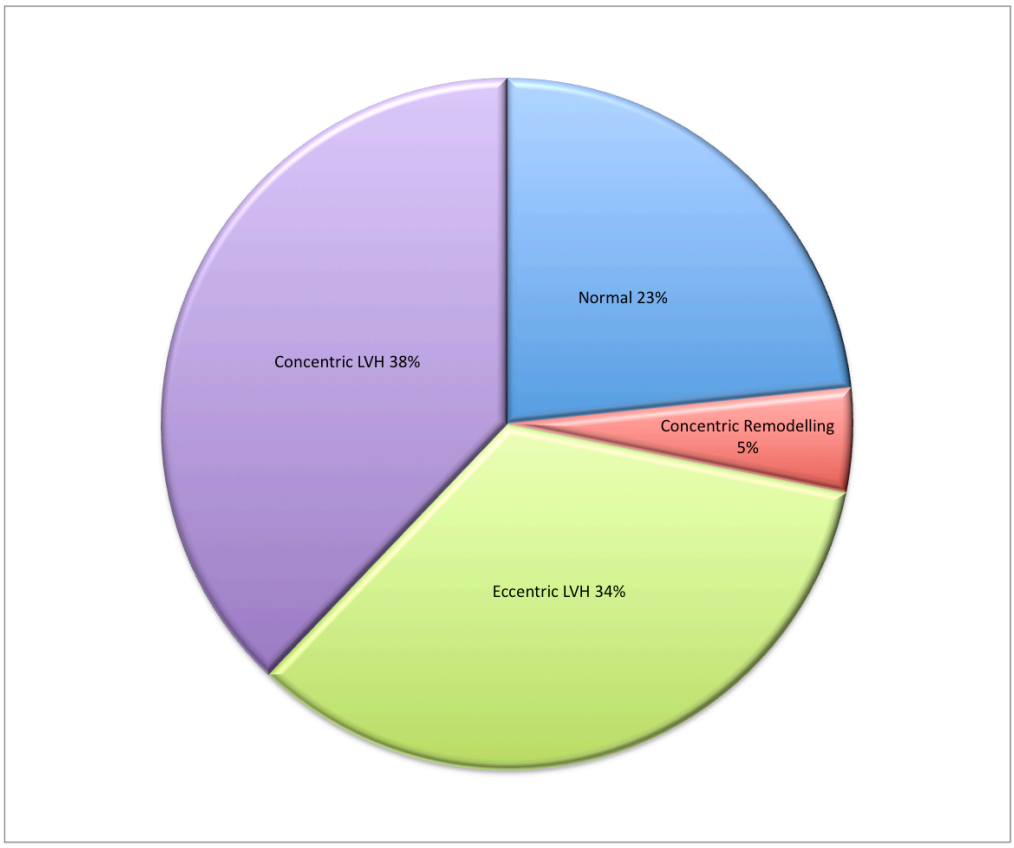
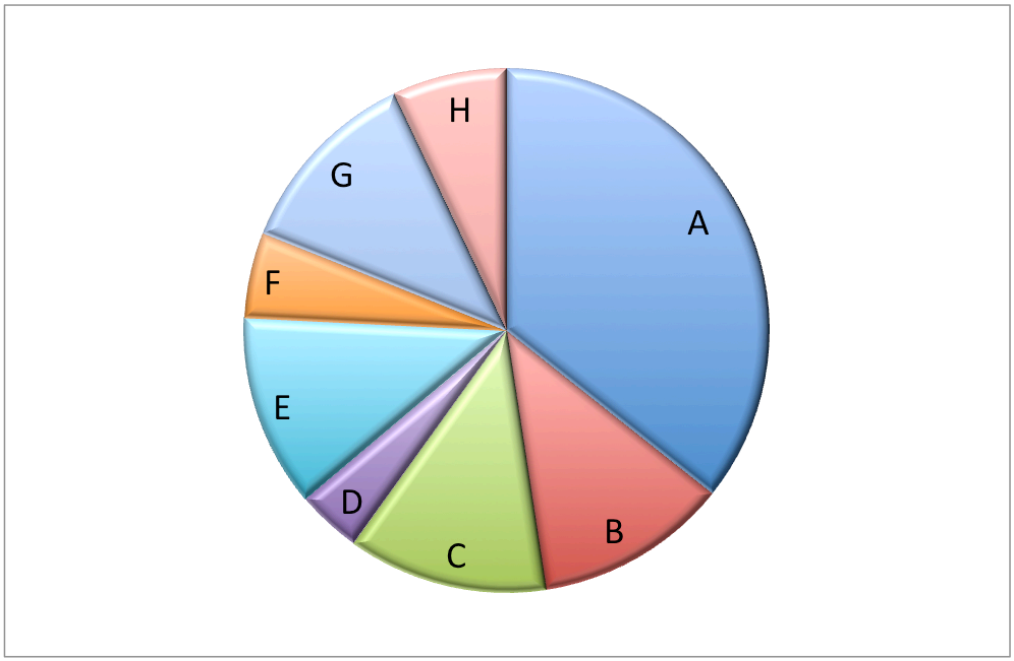


Figure 3.6: Association between history of hypertension, clinic BP (normal clinic BP <140/90) and presence or absence of LVH (indexed to height 2.7) in this study population



A History of Hypertension, High Clinic BP, LVH 36%

B History of Hypertension, High Clinic BP, No LVH 12%

C History of Hypertension, Normal Clinic BP, LVH 12%

D History of Hypertension, Normal Clinic BP, No LVH 4%

E No History of Hypertension, High Clinic BP, LVH 12%

F No History of Hypertension, High Clinic BP, No LVH 5%

G No History of Hypertension, Normal Clinic BP, LVH 12%

H No History of Hypertension, Normal Clinic BP, No LVH 7%

Figure 3.7 Association with Clinic Blood Pressure and presence or absence of LVH (indexed to Height 2.7) in the study population.

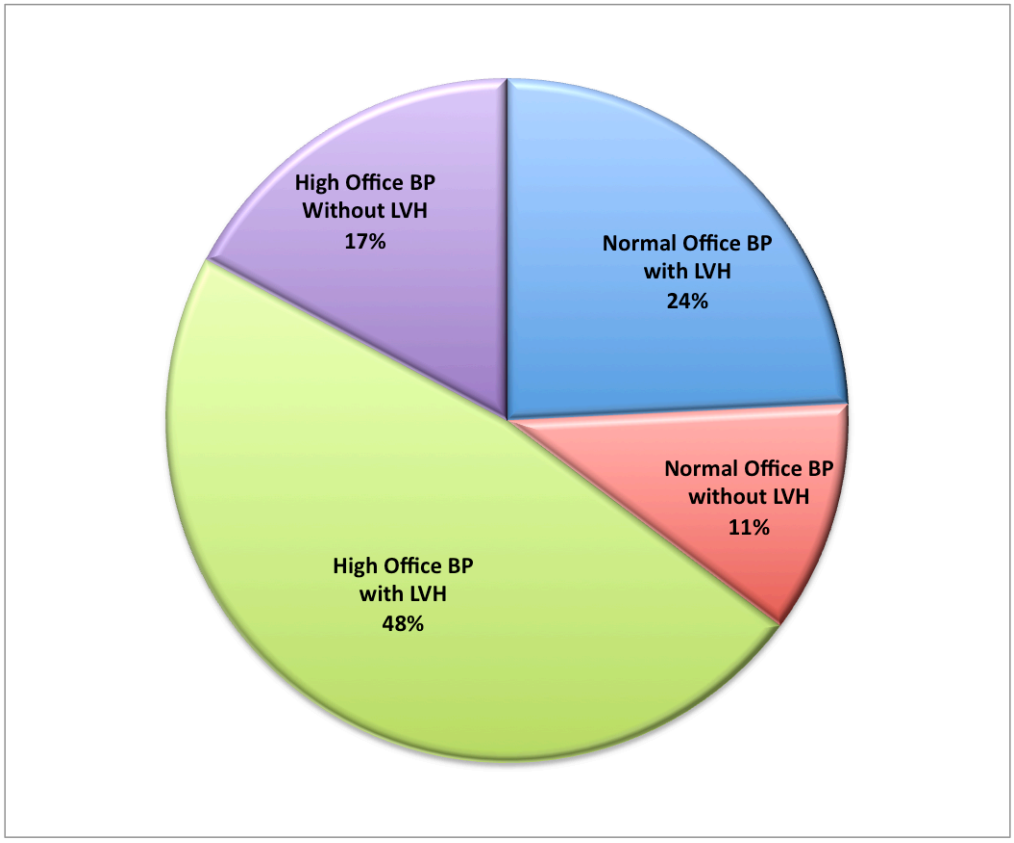
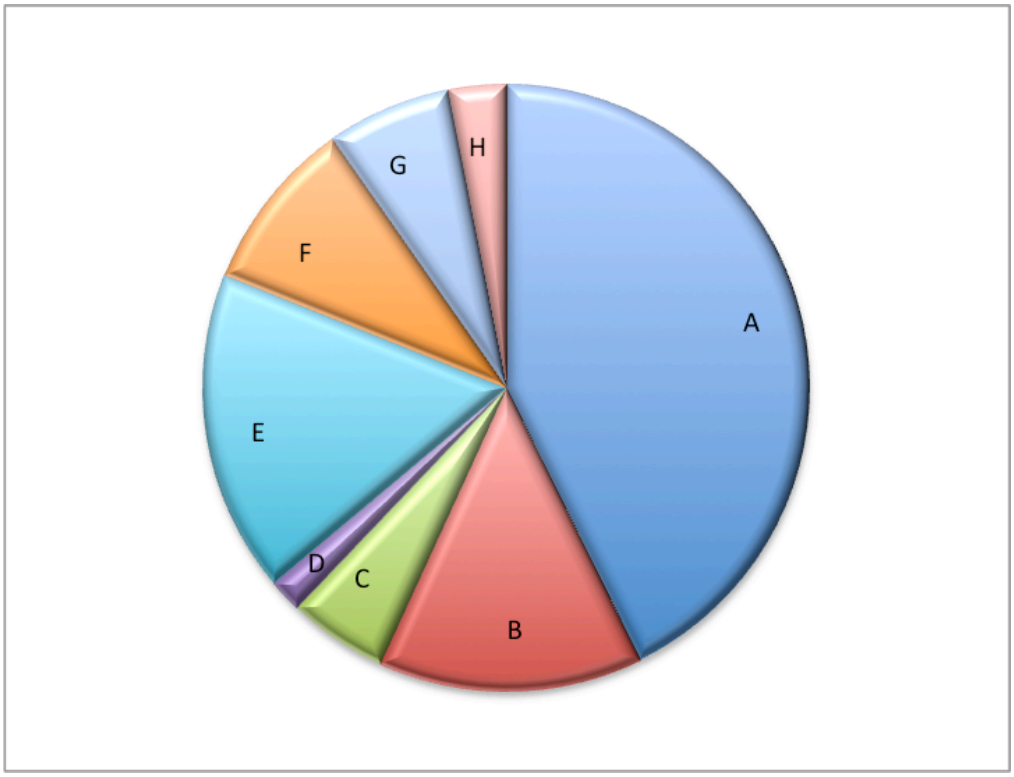


Figure 3.8: Association between history of hypertension, clinic BP (normal clinic BP<130/80) and presence or absence of LVH (indexed to height 2.7) in this study population



A History of Hypertension, High Clinic BP, LVH 43%

B History of Hypertension, High Clinic BP, No LVH 14%

C History of Hypertension, Normal Clinic BP, LVH 5%

D History of Hypertension, Normal Clinic BP, No LVH 2%

E No History of Hypertension, High Clinic BP, LVH 17%

F No History of Hypertension, High Clinic BP, No LVH 9%

G No History of Hypertension, Normal Clinic BP, LVH 7%

H No History of Hypertension, Normal Clinic BP, No LVH 3%

Figure 3.9: Association between ambulatory BP reading and the presence or absence of LVH (indexed to BSA) in the study population.

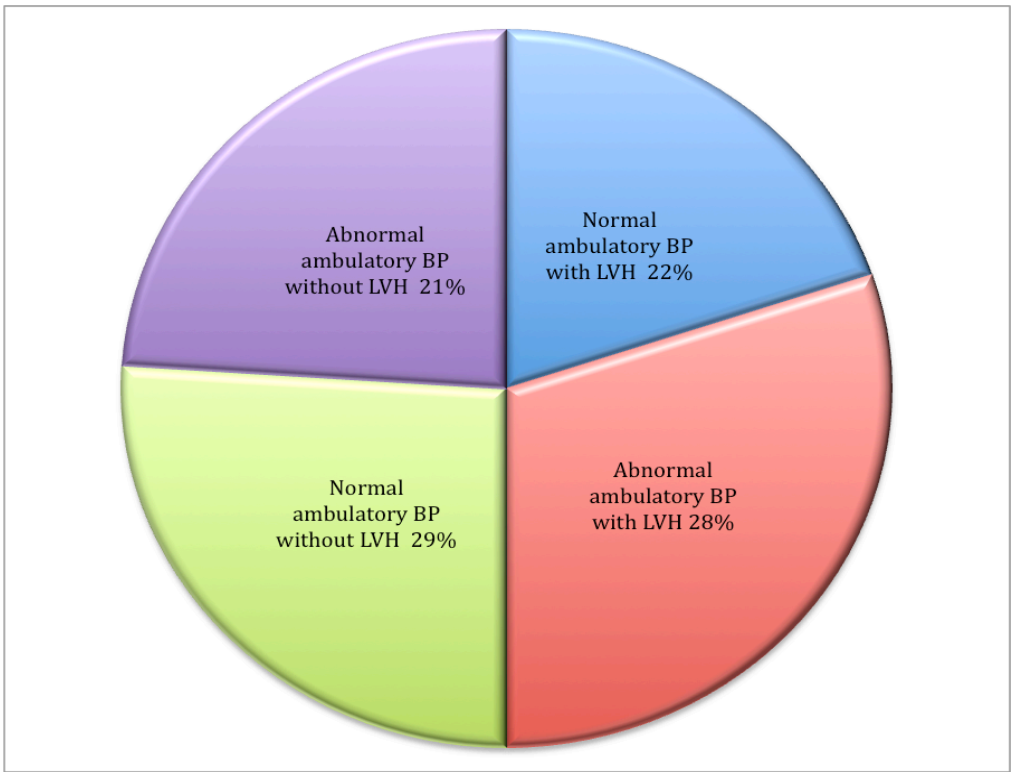
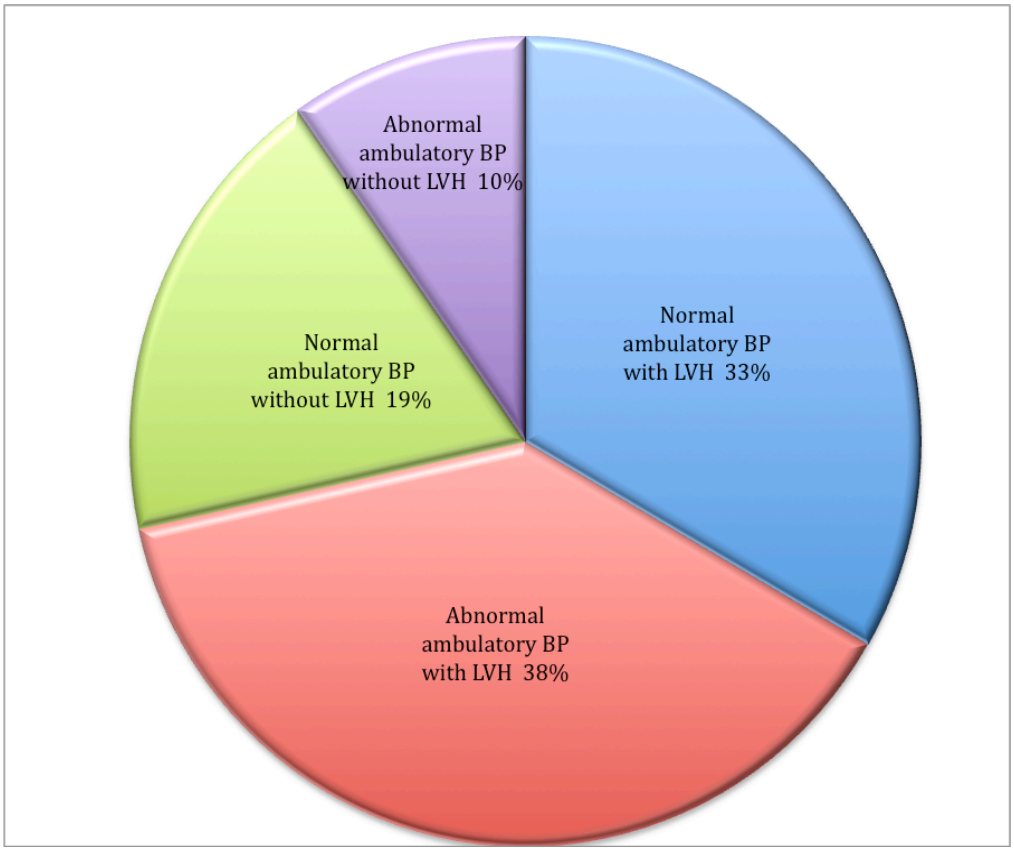


Figure 3.10: Association between ambulatory BP reading and the presence or absence of LVH (indexed to Height 2.7) in the study population.



CHAPTER 4

DISCUSSION AND FUTURE WORK

The results of this study suggest a very high prevalence (50-72%) of echo LVH in patients with peripheral arterial disease (i.e. 50% when indexed to BSA and 72% when indexed to height $^{2.7}$). Given what we know about the prognosis of LVH it is extremely likely that the high rate of cardiac death in PAD patients is attributable to some extent to this high prevalence of LVH. My other main finding is that blood pressure is an insensitive way of identifying which PAD patients have LVH since an office BP of <140/90 is found in 27-33% of all PAD patients with LVH depending on which LVH criteria are applied. Similarly a normal 24 hour BP is seen in 44-46% of all PAD patients with LVH.

Left ventricular hypertrophy is an independent predictor of cardiovascular death that is currently underestimated in current practice. In the only comparative study, the independent relative risk of LVH was 2.4 whereas the relative risk for multivessel disease was only 1.6 and for LV dysfunction was only 2.0 (7). This study in CAD patients by Liao suggests that LVH is likely to be the strongest risk factor in vascular patients. The importance of detecting and treating LVH is underscored by the fact that treatment regression of LVH independent of BP control is highly effective in reducing cardiac risk (114). Indeed, complete regression of LVH appears to reduce the risk of future cardiovascular events to normality (16).

To the best of my knowledge, this study is the first ever to look at LVH prevalence in PAD patients per se. The nearest previous study recruited hypertensive individuals with coronary disease and found that the added presence of PAD as a third disease increased the LVH prevalence from 46% to 75% (33). The fact that echo LVH is an extremely common finding in this study (at least one in two patients have this condition) suggests that current clinical practice may be ignoring what is arguably the biggest independent risk factor in a group of patients who need intensive secondary prevention. Since treating LVH is so effective, it now seems that detecting and treating LVH in PAD patients could be a new worthwhile goal with a strong chance of being able to reduce the currently high rate of cardiac death in PAD patients. It could theoretically also reduce perioperative cardiac events when the PAD patients need surgery.

In general, LVH may not get the prominence it deserves because of two misconceptions. The first misconception is the assumption that LVH only occurs in patients with Hypertension. This is not the case in normal populations and we have now found the same for PAD patients. For example, in Framingham, echo LVH occurred in 33% of men and 49% of women over the age of 70 years with a systolic BP 125-139 mmHg (10). In the Strong Heart Study, systolic blood pressure was weakly associated with LV mass and nearly 50% of LV mass variability remained unexplained (100). In this study,

a nonhypertensive office BP was found in 27-33% (depending on which LVH criteria are used) of all PAD patients with LVH.

It is worth noting that in this study LVH was indeed significantly associated with a higher office BP (151 mmHg vs 143 mmHg) and a higher 24 hr BP (137 vs 130 mmHg). However, BP was not an independent predictor in the multiple regression analysis. In addition, what is relevant for clinical practice is that 14%-24% of this study population overall had LVH and a nonhypertensive office BP and 22-33% of this population had LVH and a normal 24 hour BP. Thus, blood pressure can be used in PAD patients to identify LVH but a high BP produces a lot of false positives as far as LVH is concerned and a low BP produces a lot of false negatives. Thus, using blood pressure to predict presence of LVH in PAD patients would miss a high proportion of these patients.

A unique feature of this study is that ambulatory BP was measured in addition to office BP. It is somewhat surprising that a normal 24 hour BP missed even more LVH than an office BP. Previous studies in hypertension suggested the opposite (207-209). This may be because the aetiology of LVH in PAD patients is more complex and less dependent on the single issue of BP than it is in hypertensive patients, although this is refuted somewhat by the fact that in this study the mean BP difference between LVH and non LVH was of the same magnitude for office and 24 hour BPs. Another possibility is that the

optimum cutoff value for 24 hr BP to detect LVH may be different in PAD than in hypertension, although again this was not apparent in these data. However, the key point for clinical practice is that it has previously been suggested that an abnormal 24 hr BP should alert the clinician to look for echo LVH (210, 211). Although this may work well for hypertension, it does not appear so in PAD patients since a normal 24 hr BP (130/80 mmHg) would miss 44-46% of LVH in PAD. In fact, **Figures 3.3 and 3.4** illustrates well the dissociation between LVH and 24 hr BP in that one quarter of all PAD patients had both abnormalities, two more quarters had one abnormality without the other and the final quarter had neither abnormality.

The second general misconception regarding LVH leading to it being relatively ignored is that medications that attenuate the Renin-Angiotensin-Aldosterone-System and reduce blood pressure to target levels "cure" LVH. In fact, the high prevalence of LVH in this population despite 46% of them taking either an ACE inhibitor or an ARB tends to refute this. A more compelling argument that modulation of the RAAS does not cure LVH is that Losartan and Ramipril only reduced cardiovascular events by 14-25% in the LIFE and HOPE trials, suggesting that Angiotensin-II withdrawal is not a cure for LVH (57, 123). This leaves a lot of room for further improvement in treating LVH over and above AII withdrawal therapy. Therefore, it is appropriate to conclude that ACE inhibitors/ARB may reduce LVH but do not fully abolish it. There may be some reluctance to prescribe ACE inhibitors or

ARBs in PAD patients because they have a high incidence of coincidental renovascular disease. In fact, only 38% and 8% of PAD patients in this thesis were prescribed ACE-inhibitors or ARBs, respectively.

Various methods exist with regards to defining echocardiographic LVH. The indexation of LV mass to body height $^{2.7}$ appears to detect obesity-independent and obesity-related LVH equally well (12). For this reason, I indexed LV mass to BSA and body height $^{2.7}$ and found a difference of 22% in LVH prevalence between the two. Both methods have been prognostically validated and one recent study showed that LV mass indexed to height $^{2.7}$ carried a higher cardiac risk when compared to indexation of LV mass to BSA (relative risk of **3.3** versus **2.6** respectively) (88, 98). The main finding is not dependent on the LV mass indexation used because LVH is worryingly high (50% or 72%) regardless of whichever indexation method is employed.

This study has some limitations:

Firstly, 31% of the patients screened did not have adequate echocardiographic images to allow M-mode measurements of left ventricular dimensions to be made. This appears to be a common weakness in all echocardiographic studies but it may be larger here because this study PAD patient population had a very high incidence of smoking (current smokers 39%, ex-smokers 51%). Smoking related COPD makes it hard to obtain adequate echo images

(11, 16). Nevertheless, there was no significant differences in terms of baseline characteristics in the group between those where an M-mode LV mass was obtainable as opposed to those without an M-mode LV mass which allows us to conclude that my echo sample was truly representative of the full PAD population.

Secondly, 17% of the study population had a previous history of MI, which may have contributed to the high prevalence of abnormal LV geometry, although not in a statistically independent way. Having said this, previous MIs are also typical of a PAD population.

Thirdly, not all of my patients were at target Blood Pressure, but this appears to be a common scenario (212). This makes this study representative of the real world, even if not of the ideal world. It would be of interest to know how much renovascular disease contributes to BP in PAD patients but there is no easy screening test for it that I could have applied in such a large group of patients as here.

Overall, all three of the "limitations" described above make this study truly representative of real world PAD patients which could be viewed as strengths rather than weaknesses for an epidemiology type study such as this.

Fourthly, there was no control group to compare prevalence of LVH and blood pressure. Although, Framingham and other population studies supply this general information anyway (7, 10, 67, 91, 102, 121, 157, 213-215). I preferred to focus my efforts on studying a larger group of PAD patients than studying fewer PAD patients but adding controls. Finding controls matched for everything with the PAD cohort would have been difficult and time consuming.

Intra-observer variability was not formally assessed in this study, which may be interpreted as a limitation. Intra-observer (and inter-observer) variability were calculated in a previously published study involving echocardiographically defined LVH in patients with cardiovascular disease; and was found to be excellent (216). In this study I randomly reviewed fifty echocardiogram studies of patients with angiographically proven coronary artery disease who underwent a prior echocardiogram. A clinical risk score was calculated using various parameters to predict presence of echocardiographically determined LVH. This was validated in my PVD patient cohort. In this published study a Bland Altman plot showed a high level of agreement between myself and the other operator. The intra- and inter-observer agreement was 98%. No formal calculation of intra-observer variability was carried out for this group of patients in this Thesis. I am unable to retrospectively reanalyze the images for intra-observer variability calculations as they were stored on VHS tapes, which have subsequently been

destroyed. However, taking the excellent agreement from the above published study and the rigorous way I recorded and analysed the echo images, one would anticipate similarly good reproducibility.

Once identified, the question arises as to how we should regress LVH in these patients. This firstly involves better achieving of target BPs along with the lowering of target BPs, as recommended by the JBS2 guidelines (217). This could also mean the achievement of even lower than conventional BP targets in those with LVH (e.g. systolic BP of 120 mmHg or lower) or even an individualised BP target level that ensures full LVH regression in that individual. In the study by Simpson et al (2010) from the University of Dundee, a 9mmHg reduction in blood pressure from a normal baseline blood pressure (mean 122mmHg systolic) significantly reduced LV mass in a group of patients with LVH and normal office blood pressure (133). The meta-analysis by Law et al (2009) of blood pressure reduction showed that lowering systolic BP by 10mmHg reduces CHD events by a quarter and stroke by a third, regardless of drug used, presence or absence of target organ damage or blood pressure before treatment (218). Indeed, the relative risk reduction in events was similar across all levels of blood pressure down to 110/70 mmHg; below which there was too few data to make statistical conclusions (218). A third possibility is the addition of an aldosterone antagonist such as spironolactone or eplerenone. In the 4E study, this reduced LV mass on top of an ACE inhibitor despite the final systolic BP only being 5

mmHg lower (139 to 134 mmHg) (219). A fourth possibility which has been shown already to regress LV mass in normotensive patients is copper chelation with trientine (220-222). A new possibility to regress LVH studied recently in Dundee is allopurinol which reduces oxidative stress and LV afterload. Further studies should now address these possible ways of regressing LV mass in LVH patients with PAD (223-225).

In summary, the results of this study have major implications for patients with PAD. Firstly, the prevalence of LVH in PAD is exceedingly high. Secondly, normotensive LVH is not uncommon in stable PAD patients. Although a higher BP does point to LVH, there is a lot of overlap such that a normal office BP still occurs in 27%-33% of all PAD patients with LVH. A normal 24 hour BP occurs in even more (44-46%) PAD patients with LVH. Future studies should now address whether detecting and regressing LVH in PAD patients would be a new cost effective way to reduce the unacceptably high rate of cardiac death in such patients. Potentially it might also reduce perioperative cardiac events.

In the United Kingdom, more than 100 000 people are newly diagnosed with PAD each year. Symptomatic PAD confers a poor quality of life and is a major marker for future cardiovascular events with a worse prognosis than MI or breast cancer (6). As a result, the majority die from cardiovascular causes such as MI, stroke or arrhythmia. Strenuous efforts need to be directed

towards helping physicians, and General Practitioners in particular, highlight and address risk factor modification. Interventions include improved diet and exercise, smoking cessation programs, drug therapy, and, where necessary, blood pressure and glucose regulation.

As this study demonstrates, diagnosis and treatment of LVH in this group of patients, could potentially prove exceedingly effective in reducing cardiovascular morbidity and mortality.

Future work needs to be directed to seeing if major risk factor modification and aggressive prescribing of RAAS modulators improves the prognosis of these patients with a high cardiovascular burden and morbidity and mortality.

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Appendix

Appendix I: Example of Initial Letter inviting patient to take part in study

«Forename» «Surname»

«Address_1»
«Address_2»
«Address_3»
«Post_Code» «Letter»

Dear «Sex» «Surname»,

You attended an appointment at the Vascular Laboratory in the Hospital this year to test the blood flow in your legs. We are currently undertaking an important study with Professor Peter Stonebridge, Consultant Vascular Surgeon and Professor Allan Struthers, Professor of Cardiovascular Medicine involving people who have attended the Vascular Laboratory. I have attached an information sheet for you to read which will give you more information about the study and why we are doing it.

This study will not interfere with the care you are receiving from Professor Stonebridge or his colleagues in Ninewells Hospital. We will reimburse you fully for any travel expenses you incur attending your study appointment. If you require transport to take you to your study appointment and back I can organise this for you and we will pay for it in full.

I would be most grateful if you would return the tear-off slip below to me in the stamped addressed envelope provided. Alternatively, you can telephone me on 01382 496355 for more information.

Yours Sincerely,

Dr Gary A Wright

Please fill out with telephone number, detach slip and return in envelope provided

I *would* like an appointment for your study ☐

I *would not* like an appointment for your study ☐

I *would* like more information on the study ☐

«Forename» «Surname» Telephone Number……..

Appendix II: Example of Reminder Letter inviting patient to take part in study

«Forename» «Surname»
«Address_1»
«Address_2»
«Address_3»
«Post_Code» 10 November 2014

Dear «Sex» «Surname»,

You may remember I sent you a letter (copy attached) inviting you to take part in a study involving people like yourself with poor circulation in the legs and feet. I'm not sure if you received the letter or not, if you have I hope you don't mind me sending another one. The study will involve only one visit which will take approximately 1 to 1 ½ hours. I have attached an information sheet about the study which you can read at your leisure.

Could you please fill in the tear off slip below to indicate if you wish to take part in the study or not and if you would like me to call you with more information.

I look forward to hearing from you.

Yours Sincerely,

Dr Gary A Wright

Please fill out with telephone number, detach slip and return in envelope provided

I *would* like an appointment for your study ☐
I *would not* like an appointment for your study ☐
I *would like you to call with more information* ☐

«Forename» «Surname» Telephone Number……

Appendix III: Example of Letter detailing date of visit and directions to patients

Forename Surname
Address
Address
«Address_3»
«Post_Code» 10 November 2014

LEFT VENTRICULAR HYPERTROPHY IN PATIENTS WITH PERIPHERAL ARTERY DISEASE: THE FIRST STEPS IN ADDRESSING A PREVIOUSLY IGNORED BUT TREATABLE CULPRIT.

Dear Name,

Further to my previous letter your Date to attend the **Department of Clinical Pharmacology** for your appointment is (it will take approximately one hour):

«Day» «Date»«th» «Month» 2004 at «Time»

For the department of Clinical Pharmacology you turn left after the Metropole Café and go past wards 1&2, 3&4 and 5&6 right to the end of the corridor. Go through to the Department and ask for me, if you can not find anyone then ask the secretaries in the Department and they will come and get me.

Could you please bring with you a list of your current medication.

If you have any questions, want to change your appointment or require transport then please feel free to phone. I look forward to seeing you then.

Yours Sincerely,

Dr Gary A Wright
Clinical Research Fellow
Department of Clinical Pharmacology
Level 7
Ninewells Hospital
01382 496355

Appendix IV: Consent Form

Left Ventricular Hypertrophy in Patients with Peripheral Arterial Disease: The First Steps in Addressing a Previously Ignored but Treatable Culprit.

CONSENT FORM

NB. This form must be completed by the research subject in the presence of someone with knowledge of the research designed by the principal investigator. This may be a doctor, nurse, clinical research assistant or other member of the research team who must countersign the form as witness to the subject's signature

Please tick (✓) appropriate box

Have you read and understood the Subject Information Sheet?
Yes ☐ No ☐

Have you been given an opportunity to ask questions and further discuss this study? Yes ☐ No ☐

Have you received satisfactory answers to all of your questions?
Yes ☐ No ☐

Have you now received enough information about this study?
Yes ☐ No ☐

Who have you spoken to? Dr/Mr/Mrs/Miss
……

Do you understand that your participation is entirely voluntary?
Yes ☐ No ☐

Do you understand that you are free to withdraw from this study:

At any time?
Yes ☐ No ☐

Without having to give a reason for withdrawing?
Yes☐ No ☐

Without this affecting your present or future medical care?
Yes ☐ No ☐

Do you agree that your records in this research and supporting medical records be made available for inspection by monitors from:

NHS Tayside monitors?
Yes ☐ No ☐
Regulatory authorities?
Yes ☐ No ☐

Do you agree to take part in this study?
Yes ☐ No ☐

Do you agree to any blood used in this study being retained for use in future research?
Yes ☐ No ☐

Subject's signature …….. Date ……

Subject's name in block capital letters

……

Telephone contact (Subject) ……..(Home)

……..(Work)

Signature witnessed by …… Date

……

Witness name in block capital letters ……..

Appendix V: Echo Reporting Form

GAW003 Left Ventricular Hypertrophy in patients with peripheral vascular disease: the first steps in addressing a previously ignored but treatable culprit.

ECHOCARDIOGRAPHY

Patient Number:_____

Date of Examination:_____

Tape:_____

1. Measurements

	Mean of 3		
IVSd	_____cm	Fractional Shortening %	
LVIDd	_____cm		
PWTd	_____cm		
IVSs	_____cm		
LVIDs	_____cm	LV Mass Index (g/m^2)	
PWTs	_____cm		
LA Size	_____cm		
Aortic Root	_____cm		

2. Modified Simpsons Ejection Fraction

Mean EDV 4ch (ml)_____

Mean ESV 4ch (ml) _____ Ejection Fraction %

Mean EDV 2ch (ml) _____

Mean ESV 2ch (ml) _____

GAW003 Left Ventricular Hypertrophy in patients with peripheral vascular disease: the first steps in addressing a previously ignored but treatable culprit.

Patient Number:_____

3. LV Diastolic Assessment

	Mean
E	
A	
E/A Ratio	
Deceleration Time	
IVRT	

4. Subjective Assessment of LV, Valves and Right Heart